

COMPOUNDS FOR THE TREATMENT OF PARAMOXYVIRUS VIRAL INFECTIONS

BACKGROUND

Field

[0001] 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

[0002] 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

[0003] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Other embodiments disclosed herein relate to a compound of Formula (II), or a pharmaceutically acceptable salt thereof.

[0004] 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) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing. Other embodiments described herein relate to using one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, 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) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, 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) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing. 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) and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I), and/or Formula (II), or a pharmaceutically acceptable salt of the foregoing. 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.

[0005] 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 Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing), 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 Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing), or a pharmaceutical composition that includes one or more compounds described herein, in combination with one or more agents described herein.

DETAILED DESCRIPTION

[0006] *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.

[0007] 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.

[0008] 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

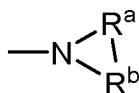
younger than 24 months of age), and Virzole® (ribavirin by aerosol, ICN pharmaceuticals) have been approved for treatment of RSV.

[0009] 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

[0010] 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.

[0011] As used herein, any "R" group(s) such as, without limitation, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, 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.

[0012] 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, 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.

[0013] 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 “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heteroalicyclyl group, the broadest range described in these definitions is to be assumed.

[0014] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that

the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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). 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.

[0019] 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 C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0020] 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 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.

[0021] 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 “heteroalicycyl” 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).

[0022] 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.

[0023] 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.

[0024] A “heteroalicycyl(alkyl)” and “heterocyclyl(alkyl)” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a heteroalicycyl(alkyl) may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl), and 1,3-thiazinan-4-yl(methyl).

[0025] “Lower alkylene groups” are straight-chained -CH₂- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), and butylene (-CH₂CH₂CH₂CH₂-). 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.”

[0026] 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.

[0027] 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.

[0028] As used herein, “acylalkyl” refers to an acyl connected, as a substituent, via a lower alkylene group. Examples include aryl-C(=O)-(CH₂)_n- and heteroaryl-C(=O)-(CH₂)_n-, where n is an integer in the range of 1 to 6.

[0029] As used herein, “alkoxyalkyl” refers to an alkoxy group connected, as a substituent, via a lower alkylene group. Examples include C₁₋₄ alkyl-O-(CH₂)_n-, wherein n is an integer in the range of 1 to 6.

[0030] As used herein, “aminoalkyl” refers to an optionally substituted amino group connected, as a substituent, via a lower alkylene group. Examples include H₂N(CH₂)_n-, wherein n is an integer in the range of 1 to 6.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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.

[0036] A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein each X is a halogen.

[0041] A “trihalomethanesulfonamido” group refers to an “X₃CS(O)₂N(R_A)-” group wherein each X is a halogen, and R_A hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl).

[0042] The term “amino” as used herein refers to a -NH₂ group.

[0043] As used herein, the term “hydroxy” refers to a -OH group.

[0044] A “cyano” group refers to a “-CN” group.

[0045] The term “azido” as used herein refers to a $-N_3$ group.

[0046] An “isocyanato” group refers to a “-NCO” group.

[0047] A “thiocyanato” group refers to a “-CNS” group.

[0048] An “isothiocyanato” group refers to an “-NCS” group.

[0049] A “carbonyl” group refers to a C=O group.

[0050] An “S-sulfonamido” group refers to a “-SO₂N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0051] An “N-sulfonamido” group refers to a “-RSO₂N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] As used herein, “-----” indicates a single or double bond, unless stated otherwise.

[0060] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example “haloalkyl” may include one or more of the same or different halogens. As another example, “C₁-C₃ alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0061] 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)).

[0062] 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.

[0063] 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).

[0064] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic

carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0069] 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).

[0070] 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.

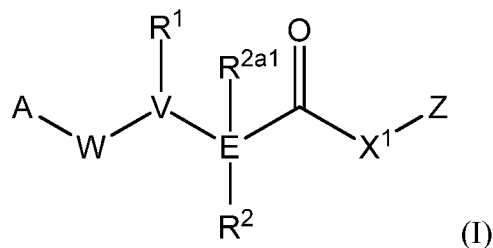
[0071] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates, and hydrates. In some embodiments, 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.

[0072] 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

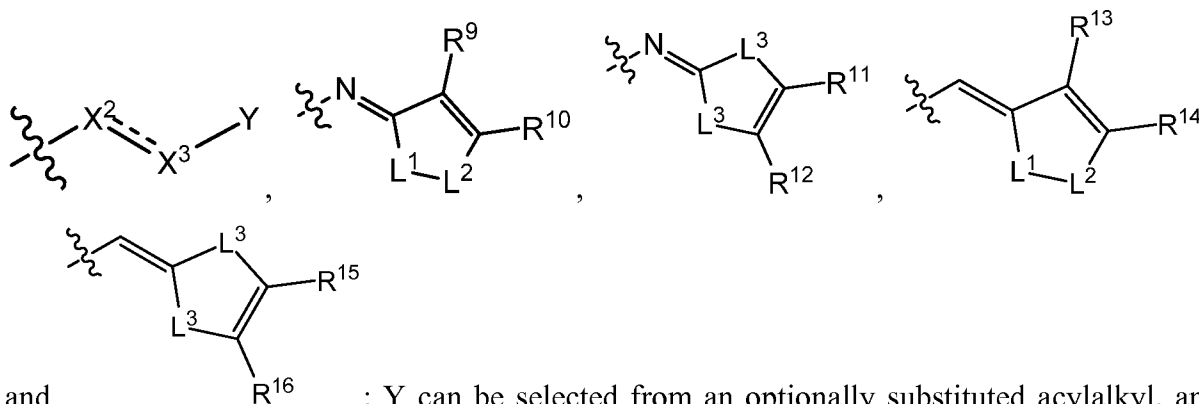
Formula (I)

[0073] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



wherein: A can be selected from an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted aryl(C₁₋₂ alkyl), an optionally substituted heteroaryl and an optionally substituted heterocyclyl; W can

be O, S, C=O, C=S, NR^{3a3} , S=O, S(=O)_2 or $-\text{C(R}^{1a1})(\text{R}^{1a2})-$; V can be N or CH; E can be C or N; provided that when E is N, then R^{2a1} is absent; Z can be selected from



and R^{16} ; Y can be selected from an optionally substituted acylalkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; ----- between X^2 and X^3 represents a single or double bond between X^2 and X^3 ; wherein when ----- is a double bond, then X^1 can be NR^{3a1} or $\text{CR}^{3a2}\text{R}^6$, X^2 can be N (nitrogen) or CR^{7a1} , and X^3 can be N (nitrogen) or CR^4 ; and when ----- is a single bond, then X^1 can be NR^{3a1} or $\text{CR}^{3a2}\text{R}^6$, X^2 can be O, NR^7 , C(=O) or $\text{C(R}^{7a2})(\text{R}^{7a3})$, and X^3 can be NR^4 , C(=O), CR^4R^8 or $\text{CH}_2\text{CH}_2\text{C(=O)}$; or X^1 , X^2 and X^3 can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O), and form a mono-cyclic ring selected from an optionally substituted mono-cyclic heteroaryl and an optionally substituted mono-cyclic heterocyclyl by joining X^1 and X^3 together; and provided that at least one of X^1 , X^2 and X^3 comprises a nitrogen atom, with the proviso that the valencies of X^1 , X^2 and X^3 can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^1 , X^2 and X^3 are uncharged; L^1 can be $-\text{C(R}^{17})_2-$, $-\text{C(R}^{18})_2\text{C(R}^{18a1})_2-$, $-\text{C(R}^{18a2})=\text{C(R}^{18a3})-$ or $-\text{C(R}^{19})_2\text{N(R}^{19a1})-$; L^2 can be $-\text{C(R}^{20})_2-$, $-\text{N(R}^{21})-$, S, or O; each L^3 can be independently $-\text{C(R}^{22})_2-$, $-\text{C(R}^{23})_2\text{C(R}^{23a1})_2-$ or $-\text{C(R}^{23a2})=\text{C(R}^{23a3})-$; provided that when L^1 is $-\text{C(R}^{19})_2\text{N(R}^{19a1})-$, then L^2 is $-\text{C(R}^{20})_2-$; R^1 can be hydrogen or an unsubstituted C_{1-4} alkyl; R^{1a1} and R^{1a2} can be each independently hydrogen, hydroxy or an unsubstituted C_{1-4} alkyl; R^2 and R^{2a1} can be each independently selected from hydrogen, an optionally substituted C_{1-4} alkyl, alkoxyalkyl, aminoalkyl, hydroxyalkyl, hydroxy, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl); or R^1 and R^2 , together with the atoms to

which they are attached, can be joined to form an optionally substituted 5-membered heterocyclic ring or an optionally substituted 6-membered heterocyclic ring; and R^{2a1} can be selected from hydrogen, an optionally substituted C_{1-4} alkyl, alkoxyalkyl, aminoalkyl, hydroxyalkyl, hydroxy, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl); R^{3a1} , R^{3a2} and R^{3a3} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^4 can be selected from hydrogen, 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 C_{3-6} cycloalkyl(C_{1-6} alkyl), an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl), an optionally substituted heterocyclyl(C_{1-6} alkyl), halo(C_{1-8} alkyl), an optionally substituted hydroxyalkyl, an optionally substituted alkoxyalkyl and cyano; R^6 , R^7 and R^{7a1} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{7a2} and R^{7a3} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^8 can be hydrogen or optionally substituted C_{1-4} alkyl; R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} and R^{16} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; or R^9 and R^{10} , R^{11} and R^{12} , R^{13} and R^{14} , and R^{15} and R^{16} , can be each independently taken together form an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and each R^{17} , each R^{18} , each R^{18a1} , R^{18a2} , R^{18a3} , each R^{19} , R^{19a1} , each R^{20} , R^{21} , each R^{22} , each R^{23} , each R^{23a1} , R^{23a2} and R^{23a3} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl.

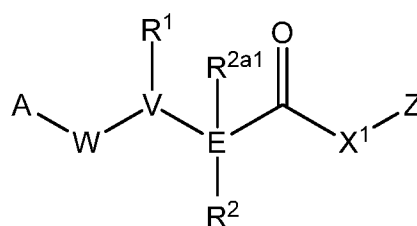
[0074] In some embodiments, ----- between X^2 and X^3 can be a double bond, X^2 can be N (nitrogen) or CR^{7a1} , and X^3 can be N (nitrogen) or CR^4 . In other embodiments, ----- between X^2 and X^3 can be a single bond, X^2 can be O, NR^7 , $C(=O)$ or $C(R^{7a2})(R^{7a3})$, and X^3 can be NR^4 , $C(=O)$, CR^4R^8 or $CH_2CH_2C(=O)$. In still other embodiments, X^1 , X^2 and X^3 can be each independently C (carbon), N (nitrogen), O (oxygen) or $C(=O)$, and form a mono-cyclic ring selected from an optionally substituted mono-cyclic heteroaryl and an optionally substituted mono-cyclic heterocyclyl by joining X^1 and X^3 together; and provided that at least one of X^1 , X^2 and X^3 comprises a nitrogen atom; with the proviso that the valencies of X^1 , X^2 and X^3 can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^1 , X^2 and X^3 are uncharged. In some embodiments,

the valencies of X^1 , X^2 and X^3 can be each independently satisfied with a substituent selected from hydrogen and an unsubstituted C_{1-4} alkyl (such as CH_3).

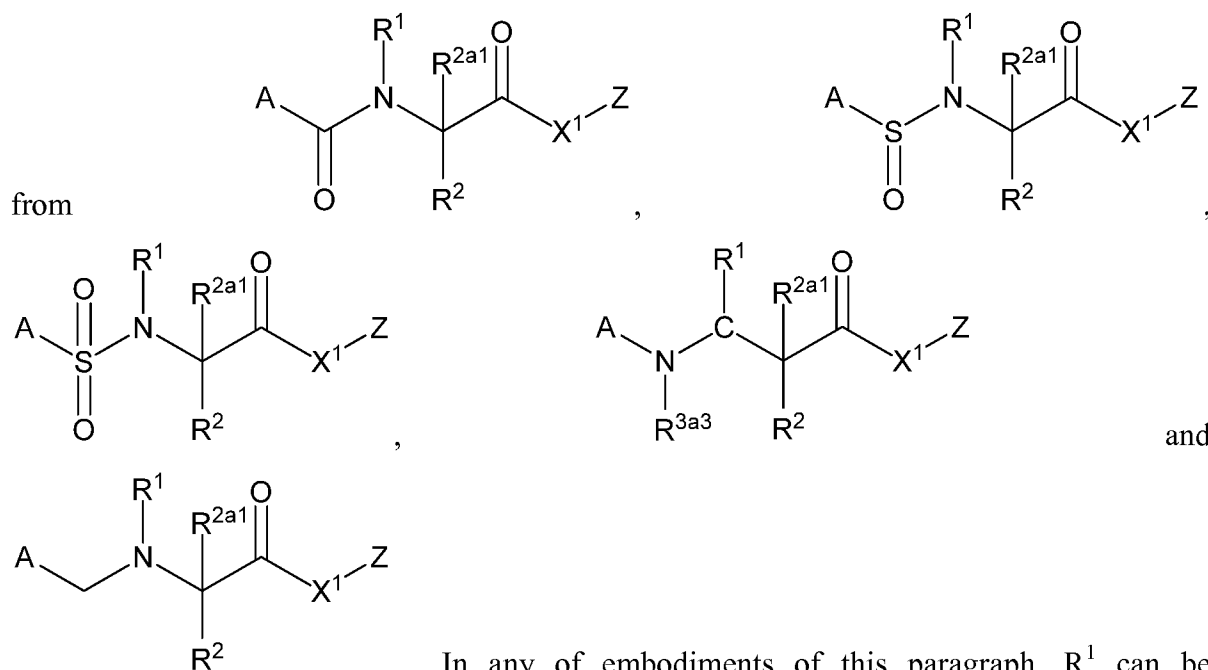
[0075] In some embodiments, W can be O (oxygen). In other embodiments, W can be S (sulfur). In still other embodiments, W can be C=O. In yet still other embodiments, W can be C=S. In some embodiments, W can be S=O. In other embodiments, W can be S(=O)₂. In still other embodiments, W can be $-C(R^{1a1})(R^{1a2})-$. In yet still other embodiments, W can be NR^{3a3} . In some embodiments, both R^{1a1} and R^{1a2} can be hydrogen. In other embodiments, at least one of R^{1a1} and R^{1a2} can be hydrogen and the other of R^{1a1} and R^{1a2} can be hydroxy or an unsubstituted C_{1-4} alkyl. In some embodiments, W can be $-CH_2-$. In other embodiments, W can be NH. In still other embodiments, W can be NR^{3a3} , wherein R^{3a3} can be an unsubstituted C_{1-4} alkyl.

[0076] In some embodiments, V can be N (nitrogen). In some embodiments, V- R^1 can be NH. In other embodiments, V- R^1 can be NR^1 , wherein R^1 can be an unsubstituted C_{1-4} alkyl. In some embodiments, V can be CH. In some embodiments, V- R^1 can be CH_2 . In other embodiments, V- R^1 can be CHR^1 , wherein R^1 can be unsubstituted C_{1-4} alkyl.

[0077] In some embodiments, E can be C. In some embodiments, when E is C, at least one of R^{2a1} and R^2 can be hydrogen and the other of R^{2a1} and R^2 can be hydroxy, an optionally substituted C_{1-4} alkyl or an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, when E is C, at least one of R^{2a1} and R^2 can be hydrogen and the other of R^{2a1} and R^2 can be an unsubstituted C_{1-4} alkyl or an optionally substituted benzyl. In some embodiments, $ER^{2a1}R^2$ can be CH_2 . In some embodiments, E can be N, provided that R^{2a1} is absent. In some embodiments, E- R^2 can be NH. In other embodiments, E- R^2 can be NR^2 , wherein R^2 can be hydroxy, an optionally substituted C_{1-4} alkyl or an optionally substituted aryl(C_{1-6} alkyl). For example, E can be NCH_3 , NCH_2CH_3 , $NCH_2CH_2CH_3$, $NCHCH_3CH_3$.



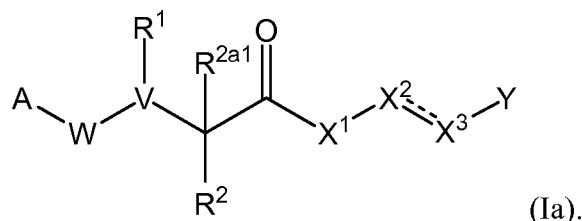
[0078] In some embodiments, can be selected



. In any of embodiments of this paragraph, R^1 can be hydrogen. In any of the embodiments of this paragraph, R^1 can be an unsubstituted C_{1-4} alkyl. In any of the embodiments of this paragraph, both R^2 and R^{2a1} can be hydrogen. In any of the embodiments of this paragraph, R^2 can be hydrogen and R^{2a1} can be an unsubstituted C_{1-4} alkyl, a substituted C_{1-4} alkyl, hydroxy or an optionally substituted benzyl. In any of the embodiments of this paragraph, R^{2a1} can be hydrogen, and R^1 and R^2 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.

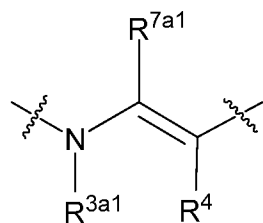
Formula (Ia)

[0079] In some embodiments, a compound of Formula (I), or pharmaceutically acceptable salt thereof, can be represented by Formula (Ia):

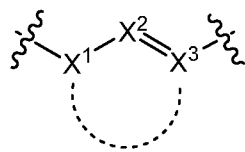


[0080] In some embodiments of Formula (Ia), ----- between X^2 and X^3

represents a double bond and can be or



. In some embodiments, X^1 , X^2 and X^3 can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O), and form a mono-cyclic ring having the

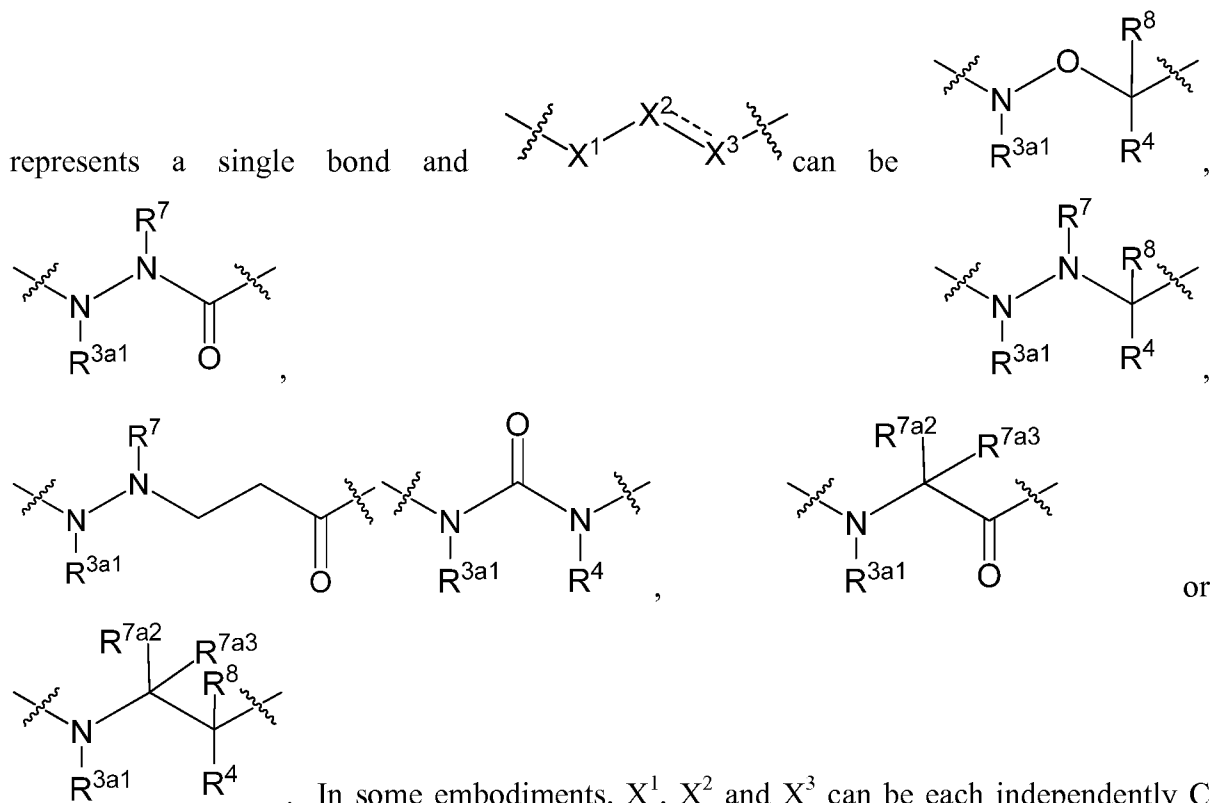


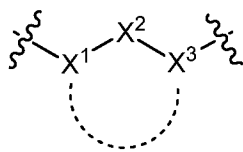
structure and selected from an optionally substituted mono-cyclic heteroaryl and an optionally substituted mono-cyclic heterocyclyl by joining X^1 and X^3 together; provided that at least one of X^1 , X^2 and X^3 comprises a nitrogen atom; with the proviso that the valencies of X^1 , X^2 and X^3 can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^1 , X^2 and X^3 are uncharged. In any of embodiments of this paragraph, W can be C(=O) and V can be N (nitrogen). In any of embodiments of this paragraph, W can be C(=S) and V can be N (nitrogen).

[0081] In some embodiments, ----- between X^2 and X^3 can be a double bond, X^1 can be NR^{3a1} , X^2 can be N (nitrogen) and X^3 can be CR^4 . In some embodiments, ----- between X^2 and X^3 can be a double bond, X^1 can be NH, X^2 can be N, and X^3 can be CH. In other embodiments, ----- between X^2 and X^3 can be a double bond, X^1 can be NR^{3a1} , X^2

can be N, and X^3 can be CR^4 , wherein R^{3a1} can be hydrogen or an unsubstituted C_{1-6} alkyl, and R^4 can be an unsubstituted C_{1-6} alkyl. In still other embodiments, ----- between X^2 and X^3 can be a double bond, X^1 can be NR^{3a1} , X^2 can be N, and X^3 can be CR^4 , wherein R^{3a1} can be hydrogen or an unsubstituted C_{1-6} alkyl, and R^4 can be cyano, an optionally substituted C_{1-6} alkyl (for example, a cyano substituted C_{1-6} alkyl), an unsubstituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an unsubstituted C_{3-6} cycloalkyl, an unsubstituted C_{3-6} cycloalkyl(C_{1-4} alkyl), a hydroxy (C_{1-4} alkyl), an unsubstituted C_{1-4} alkoxyalkyl a halo(C_{1-4} alkyl), an optionally substituted phenyl or an optionally substituted heteroaryl. In yet still other embodiments, ----- between X^2 and X^3 can be a double bond, X^1 can be NR^{3a1} , X^2 can be N, and X^3 can be CR^4 , wherein R^4 can be an hydrogen or an unsubstituted C_{1-6} alkyl. In some embodiments, ----- between X^2 and X^3 can be a double bond, X^1 can be NR^{3a1} , X^2 can be CR^{7a1} , and X^3 can be CR^4 , such as X^1 can be NH, X^2 can be CH, and X^3 can be CH.

[0082] In some embodiments of Formula (Ia), ----- between X^2 and X^3



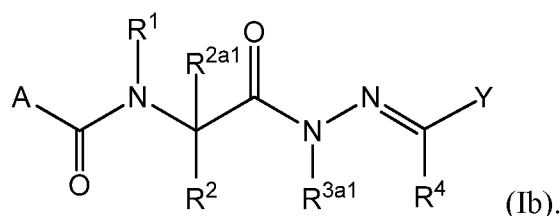


structure and selected from an optionally substituted mono-cyclic heteroaryl and an optionally substituted mono-cyclic heterocyclyl by joining X^1 and X^3 together; provided that at least one of X^1 , X^2 and X^3 comprises a nitrogen atom; with the proviso that the valencies of X^1 , X^2 and X^3 can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^1 , X^2 and X^3 are uncharged. In any of the embodiments of this paragraph, W can be C(=O), V can be N (nitrogen) and E can be C (carbon).

[0083] In some embodiments, ----- between X^2 and X^3 can be a single bond, X^1 can be NH, X^2 can be NH, and X^3 can be CH_2 . In other embodiments, ----- between X^2 and X^3 can be a single bond, X^1 can be NH, X^2 can be CH_2 , and X^3 can be CHR^4 , wherein R^4 can be H, an optionally substituted C_{1-4} alkyl or C_{1-4} alkoxyalkyl. In still other embodiments, ----- between X^2 and X^3 can be a single bond, X^1 can be NR^{3a1} , X^2 can be O, and X^3 can be CH_2 , wherein R^{3a1} can be an unsubstituted C_{1-4} alkyl. In yet still embodiments, ----- between X^2 and X^3 can be a single bond, X^1 can be NH, X^2 can be NR^7 , and X^3 can be C(=O), wherein R^7 can be hydrogen or an unsubstituted C_{1-4} alkyl. In some embodiments, ----- between X^2 and X^3 can be a single bond, X^1 can be NR^{3a1} , X^2 can be C(=O), and X^3 can be NR^4 , wherein R^{3a1} can be an unsubstituted C_{1-4} alkyl and R^4 can be an unsubstituted C_{1-4} alkyl or alkoxyalkyl. In other embodiments, ----- between X^2 and X^3 can be a single bond, X^1 can be NH, X^2 can be CH_2 , and X^3 can be C(=O).

Formula (Ib)

[0084] In some embodiments, a compound of Formula (I) can be represented by Formula (Ib):

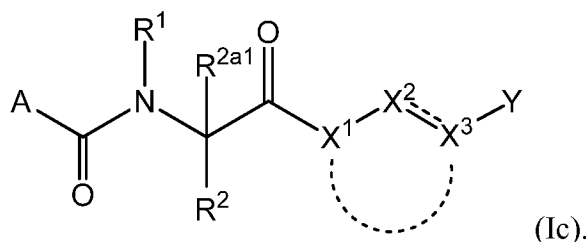


[0085] In some embodiments of Formula (Ib), R^{3a1} can be hydrogen. In other embodiments of Formula (Ib), R^{3a1} can be an unsubstituted C_{1-4} alkyl.

[0086] In some embodiments of Formula (Ib), R^4 can be selected from hydrogen, 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 (for example, phenyl), an optionally substituted heteroaryl (for example, thiophenyl or pyridinyl), an optionally substituted heterocyclyl, an optionally substituted C_{3-6} cycloalkyl(C_{1-6} alkyl), an optionally substituted aryl(C_{1-6} alkyl) (for example, benzyl), an optionally substituted heteroaryl(C_{1-6} alkyl), an optionally substituted heterocyclyl(C_{1-6} alkyl), halo(C_{1-8} alkyl), an optionally substituted hydroxyalkyl, an optionally substituted alkoxyalkyl and cyano.

Formula (Ic)

[0087] In some embodiments, a compound of Formula (I) can be represented by Formula (Ic):



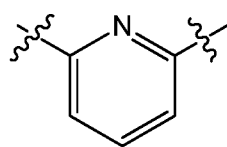
wherein the dotted curved line between X^1 and X^3 indicates a mono-cyclic ring selected from an optionally substituted mono-cyclic heteroaryl and an optionally substituted mono-cyclic heterocyclyl by joining X^1 and X^3 together; wherein X^1 , X^2 and X^3 can be each independently C (carbon), N (nitrogen), O (oxygen) or C(=O); and provided that at least one of X^1 , X^2 and X^3 comprises a nitrogen atom; with the proviso that the valencies of X^1 , X^2 and X^3 can be each independently satisfied with a substituent selected from hydrogen and an optionally substituted C_{1-4} alkyl; and X^1 , X^2 and X^3 are uncharged. In some embodiments, the valencies of X^1 , X^2 and X^3 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^1 , X^2 and X^3 can be each independently satisfied with hydrogen or methyl.

[0088] In some embodiments of Formula (Ic), the mono-cyclic ring can be an optionally substituted 5 membered heteroaryl. In other embodiments of Formula (Ic), the mono-cyclic ring can be an optionally substituted 5 membered heterocyclyl. In still other

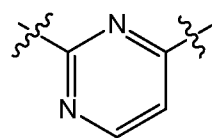
embodiments of Formula (Ic), the mono-cyclic ring can be an optionally substituted 6 membered heteroaryl. In yet still other embodiments of Formula (Ic), the mono-cyclic ring can be an optionally substituted 6 membered heterocyclyl.

[0089] In some embodiments of Formula (Ic), X^1 can be C, X^2 can be N and X^3 can be C. In some embodiments of Formula (Ic), when X^1 can be C, X^2 can be N and X^3 can be C, the mono-cyclic ring can be an optionally substituted mono-cyclic heteroaryl ring. In other embodiments of Formula (Ic), when X^1 can be C, X^2 can be N and X^3 can be C, the mono-cyclic ring can be an optionally substituted mono-cyclic heterocyclyl.

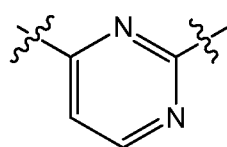
[0090] In some embodiments of Formula (Ic), when X^1 can be C, X^2 can be N and X^3 can be C, the mono-cyclic ring can be selected from an optionally substituted



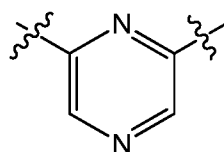
, an optionally substituted



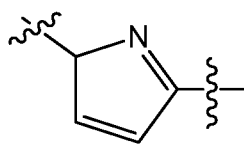
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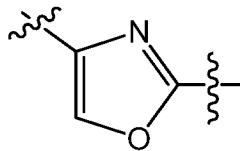
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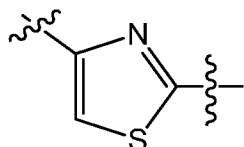
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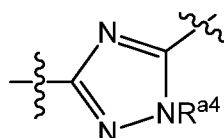
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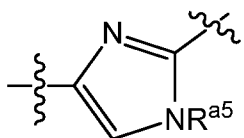
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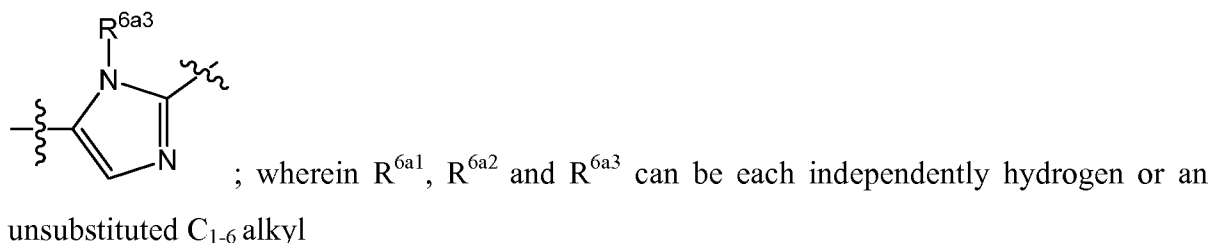
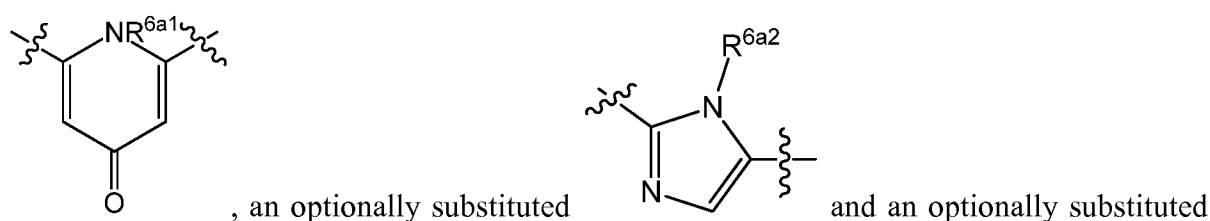


and an optionally substituted



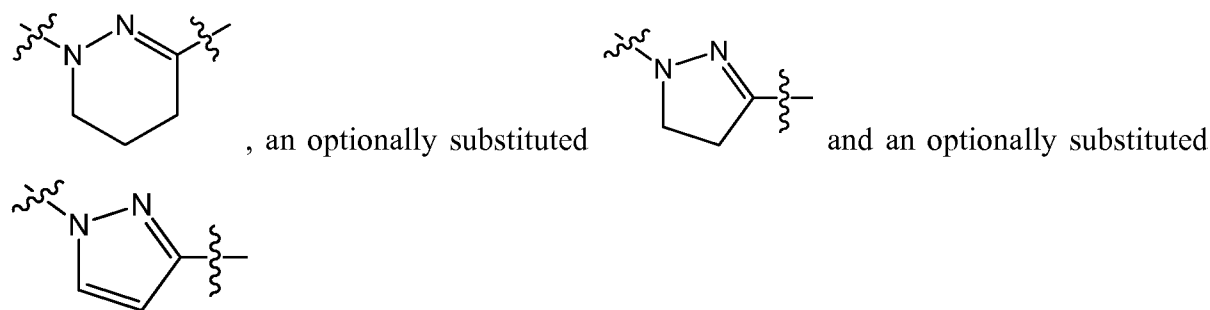
; wherein R^{a4} and R^{a5} can be each independently hydrogen or an unsubstituted C_{1-6} alkyl.

[0091] In some embodiments of Formula (Ic), when X^1 can be C, X^2 can be N and X^3 can be C, the mono-cyclic ring can be selected from an optionally substituted



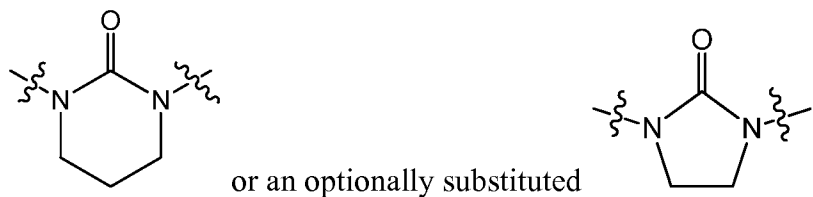
[0092] In some embodiments of Formula (Ic), X^1 can be N, X^2 can be N and X^3 can be C. In some embodiments of Formula (Ic), when X^1 can be N, X^2 can be N and X^3 can be C, the mono-cyclic ring or can be an optionally substituted mono-cyclic heteroaryl ring. In other embodiments of Formula (Ic), when X^1 can be N, X^2 can be N and X^3 can be C, the mono-cyclic ring can be an optionally substituted mono-cyclic heterocyclyl ring.

[0093] In some embodiments of Formula (Ic), when X^1 can be N, X^2 can be N and X^3 can be C, the mono-cyclic ring can be selected from an optionally substituted



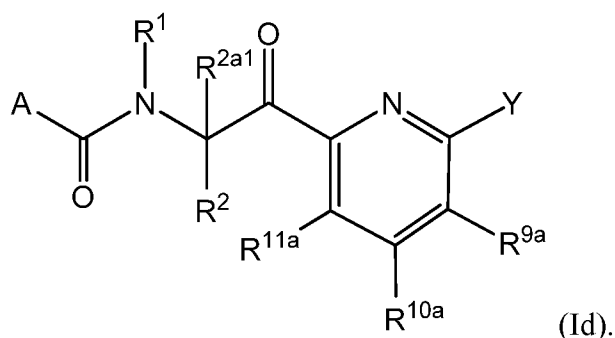
[0094] In some embodiments of Formula (Ic), X^1 can be N, X^2 can be $C(=O)$ and X^3 can be N. In some embodiments of Formula (Ic), when X^1 can be N, X^2 can be $C(=O)$ and X^3 can be N, the mono-cyclic ring can be an optionally substituted mono-cyclic heteroaryl ring. In other embodiments of Formula (Ic), when X^1 can be N, X^2 can be $C(=O)$ and X^3 can be N, the mono-cyclic ring can be an optionally substituted mono-cyclic heterocyclyl.

[0095] In some embodiments of Formula (Ic), when X^1 can be N, X^2 can be C(=O) and X^3 can be N, the mono-cyclic ring can be selected from an optionally substituted



Formula (Id)

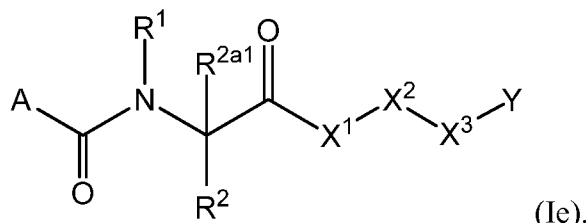
[0096] In some embodiments, a compound of Formula (I) can be represented by Formula (Id):



wherein R^{9a} , R^{10a} and R^{11a} 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 and an optionally substituted C-carboxy. In some embodiments, at least one of R^{9a} , R^{10a} and R^{11a} can be a C_{1-4} alkoxy. In some embodiments, R^{9a} can be a C_{1-4} alkoxy, and R^{10a} and R^{11a} can be both hydrogen.

Formula (Ie)

[0097] In some embodiments, a compound of Formula (I) can be represented by Formula (Ie):

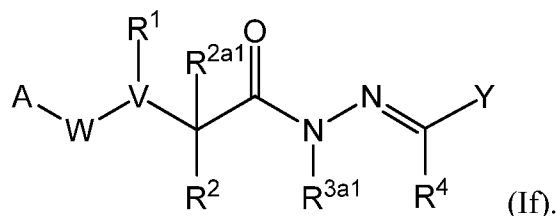


[0098] In some embodiments of Formula (Ie), X^1 can be NR^{3a1} , X^2 can be NR^7 , and X^3 can be CR^4R^8 . In other embodiments of Formula (Ie), X^1 can be NR^{3a1} , X^2 can be $CR^{7a2}R^{7a3}$, and X^3 can be CR^4R^8 . In still other embodiments of Formula (Ie), X^1 can be NR^{3a1} , X^2 can be O, and X^3 can be CR^4R^8 . In some embodiments, including those of this paragraph, R^8 can be hydrogen. In other embodiments, including those of this paragraph, R^8 can be an optionally substituted C_{1-4} alkyl. In some embodiments, including those of this paragraph, R^8 can be an unsubstituted C_{1-4} alkyl.

[0099] In some embodiments of Formula (Ie), X^1 can be NR^{3a1} , X^2 can be NR^7 , and X^3 can be $C(=O)$. In other embodiments of Formula (Ie), X^1 can be NR^{3a1} , X^2 can be $C(=O)$, and X^3 can be NR^4 . In still other embodiments of Formula (Ie), X^1 can be NR^{3a1} , X^2 can be $CR^{7a2}R^{7a3}$, and X^3 can be $C(=O)$. In yet still other embodiments of Formula (Ie), X^1 can be NR^{3a1} , X^2 can be NR^7 , and X^3 can be $CH_2CH_2C(=O)$.

Formula (If)

[0100] In some embodiments, a compound of Formula (I) can be represented by Formula (If):



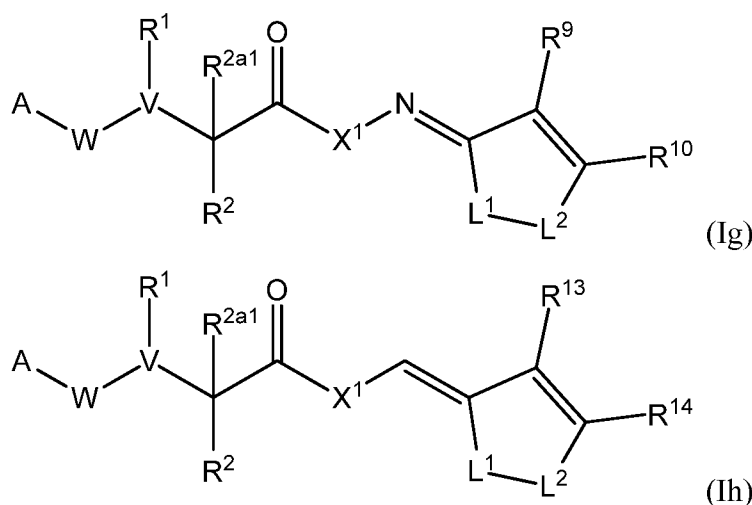
wherein: W can be O (oxygen), S (sulfur), C=S, NR^{3a3} , S=O, $S(=O)_2$ or $-C(R^{1a1})(R^{1a2})-$, and V can be N or CH.

[0101] In some embodiments of Formula (If), R^{3a1} can be hydrogen. In other embodiments of Formula (If), R^{3a1} can be unsubstituted C_{1-4} alkyl.

[0102] In some embodiments of Formula (If), R^4 can be selected from hydrogen, 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 (for example, phenyl), an optionally substituted heteroaryl (for example, thiophenyl or pyridinyl), an optionally substituted heterocyclyl, an optionally substituted C_{3-6} cycloalkyl(C_{1-6} alkyl), an optionally substituted aryl(C_{1-6} alkyl) (for example, benzyl), an optionally substituted heteroaryl(C_{1-6} alkyl), an optionally substituted heterocyclyl(C_{1-6} alkyl), halo(C_{1-8} alkyl), an optionally substituted hydroxyalkyl, an optionally substituted alkoxyalkyl and cyano.

Formulae (Ig) and (Ih)

[0103] In some embodiments, a compound of Formula (I) can be represented by Formula (Ig) or Formula (Ih):



[0104] In some embodiments, W of Formula (Ig) or Formula (Ih) can be $C(=O)$.

[0105] In some embodiments, V of Formula (Ig) or Formula (Ih) can be N (nitrogen).

[0106] In some embodiments, X^1 of Formula (Ig) or Formula (Ih) can be NR^{3a1} , such as NH.

[0107] In some embodiments of Formulae (Ig) and (Ih), L^1 can be $-C(R^{18})_2C(R^{18a1})_2-$ and L^2 can be $-C(R^{20})_2-$. In some embodiments, L^1 can be $-CH_2CH_2-$ and L^2 can be $-CH_2-$. In other embodiments of Formulae (Ig) and (Ih), L^1 can be $-C(R^{17})_2-$ and L^2 can be $-C(R^{20})_2-$, such as L^1 can be $-CH_2-$ and L^2 can be $-CH_2-$. In still other embodiments of Formulae (Ig) and (Ih), L^1 can be $-C(R^{18})_2C(R^{18a1})_2-$ and L^2 can be selected from $-N(R^{21})-$, S and O. In some embodiments, L^1 can be $-CH_2CH_2-$ and L^2 can be $-NH-$. In other embodiments, L^1 can be $-CH_2CH_2-$ and L^2 can be $-O-$. In still other embodiments, L^1 can be $-CH_2CH_2-$ and L^2 can be $-S-$. In yet still other embodiments of Formulae (Ig) and (Ih), L^1 can be $-C(R^{19})_2N(R^{19a1})-$ and L^2 can be $-C(R^{20})_2-$ (for example, L^1 can be $-CH_2N(CH_2CH_3)-$ and L^2 can be $-CH_2-$).

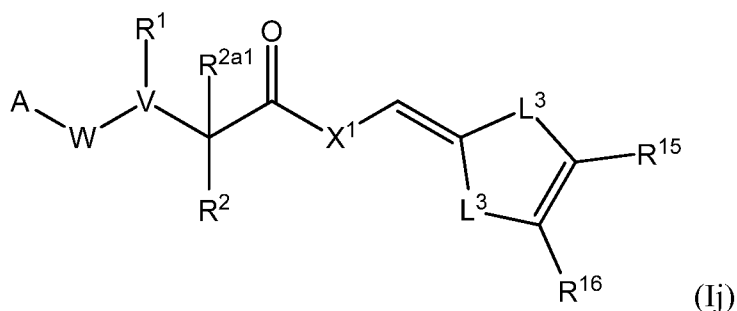
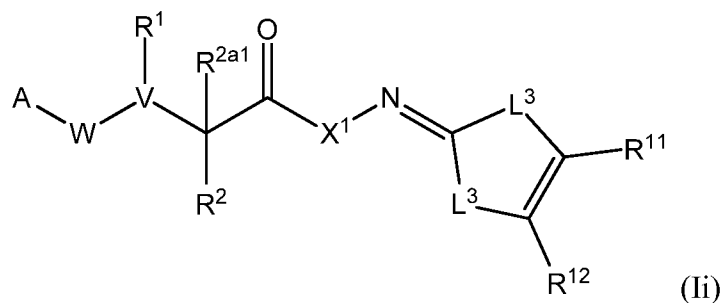
[0108] In some embodiments of Formula (Ig), R^9 and R^{10} can be each joined together with the atoms to which they are attached to form an optionally substituted aryl. For example, the optionally substituted phenyl can be substituted one or more times. In other embodiments of Formula (Ig), the optionally substituted aryl can be an unsubstituted aryl. In some embodiments of Formula (Ig), R^9 and R^{10} can be each joined together with the atoms to which they are attached to form an optionally substituted heteroaryl. In some embodiments of Formula (Ig), R^9 and R^{10} can be each joined together with the atoms to which they are attached to form an optionally substituted heterocyclyl.

[0109] In some embodiments of Formula (Ih), R^{13} and R^{14} can be each joined together with the atoms to which they are attached to form an optionally substituted aryl. For example, the optionally substituted phenyl can be substituted one or more times. In some embodiments of Formula (Ih), the optionally substituted aryl (such as phenyl) can be substituted with one or more substituents selected from halo, alkyl and alkoxy. In other embodiments, the optionally substituted aryl can be an unsubstituted aryl. In some embodiments of Formula (Ih), R^{13} and R^{14} can be each joined together with the atoms to which they are attached to form an optionally substituted heteroaryl. Suitable examples of optionally substituted heteroaryls include, but are not limited to, an optionally substituted thiophene, an optionally substituted benzothiophene, or an optionally substituted indole. In some embodiments, the optionally substituted heteroaryl can be substituted with one or more substituents selected from halo, alkyl and alkoxy. In some embodiments, the heteroaryl can be unsubstituted. In some embodiments of Formula (Ih), R^{13} and R^{14} can be each joined

together with the atoms to which they are attached to form an optionally substituted heterocyclyl.

Formulae (Ii) and (Ij)

[0110] In some embodiments, a compound of Formula (I) can be represented by Formula (Ii) or Formula (Ij):



[0111] In some embodiments, W of Formula (Ii) or Formula (Ij) can be C(=O).

[0112] In some embodiments, V of Formula (Ii) or Formula (Ij) can be N (nitrogen).

[0113] In some embodiments, X¹ of Formula (Ii) or Formula (Ij) can be NR^{3a1}, such as NH.

[0114] In some embodiments of Formula (Ii) or Formula (Ij), L³ can be -C(R²²)₂-, for example, -CH₂-.

[0115] In some embodiments of Formula (Ii), R¹¹ and R¹² can be each joined together with the atoms to which they are attached to form an optionally substituted aryl. For example, the optionally substituted phenyl can be substituted one or more times. In other embodiments, the optionally substituted aryl can be an unsubstituted aryl. In some embodiments of Formula (Ii), R¹¹ and R¹² can be each joined together with the atoms to which they are attached to form an optionally substituted heteroaryl. In some embodiments

of Formula (Ii), R^{11} and R^{12} can be each joined together with the atoms to which they are attached to form an optionally substituted heterocyclyl.

[0116] In some embodiments of Formula (Ij), R^{15} and R^{16} can be each joined together with the atoms to which they are attached to form an optionally substituted aryl. For example, the optionally substituted phenyl can be substituted one or more times. In some embodiments, the optionally substituted aryl (such as phenyl) can be substituted with one or more substituents selected from halo, alkyl and alkoxy. In other embodiments, the optionally substituted aryl can be an unsubstituted aryl. In some embodiments of Formula (Ij), R^{15} and R^{16} can be each joined together with the atoms to which they are attached to form an optionally substituted heteroaryl. Suitable examples of optionally substituted heteroaryls include, but are not limited to, an optionally substituted thiophene, an optionally substituted benzothiophene, or an optionally substituted indole. In some embodiments, the optionally substituted heteroaryl can be substituted with one or more substituents selected from halo, alkyl and alkoxy. In some embodiments, the heteroaryl can be unsubstituted. In some embodiments of Formula (Ij), R^{15} and R^{16} can be each joined together with the atoms to which they are attached to form an optionally substituted heterocyclyl.

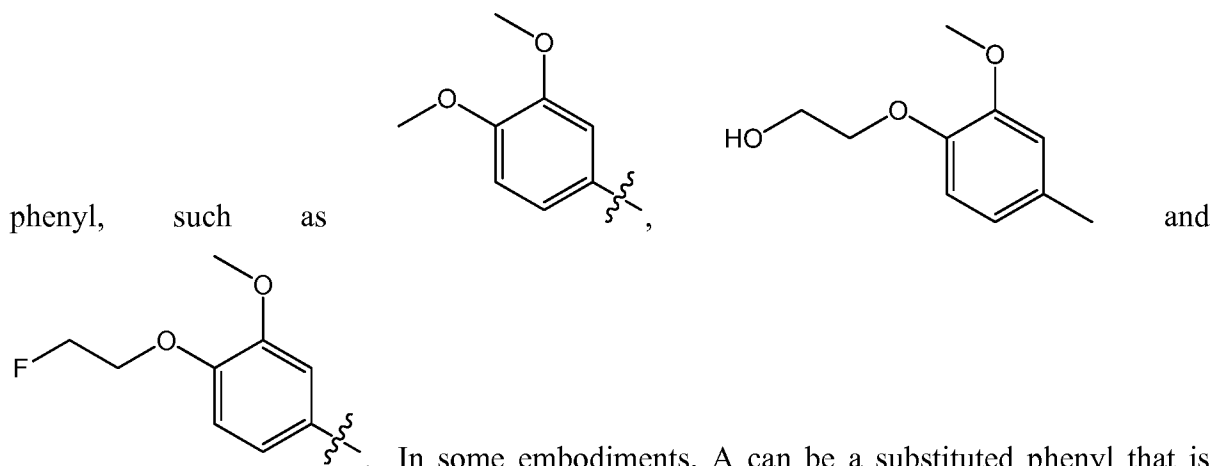
[0117] In some embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^1 can be hydrogen. In some embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^1 can be an unsubstituted C_{1-4} alkyl.

[0118] In some embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), both R^2 and R^{2a1} can be hydrogen. In other embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^2 can be hydrogen and R^{2a1} can be an unsubstituted C_{1-4} alkyl. In still other embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^2 can be hydrogen and R^{2a1} can be a substituted C_{1-4} alkyl. In yet still other embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^2 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), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^2 can be hydrogen and R^{2a1} can be an alkoxyalkyl, an aminoalkyl or a hydroxyalkyl. In other embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^2 can be hydrogen and R^{2a1} can be hydroxy. In still other embodiments of Formulae (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) and/(Ij), R^{2a1} can be

hydrogen, and R^1 and R^2 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, piperidinyl).

[0119] In some embodiments, A can be substituted. In other embodiments, A can be unsubstituted.

[0120] 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

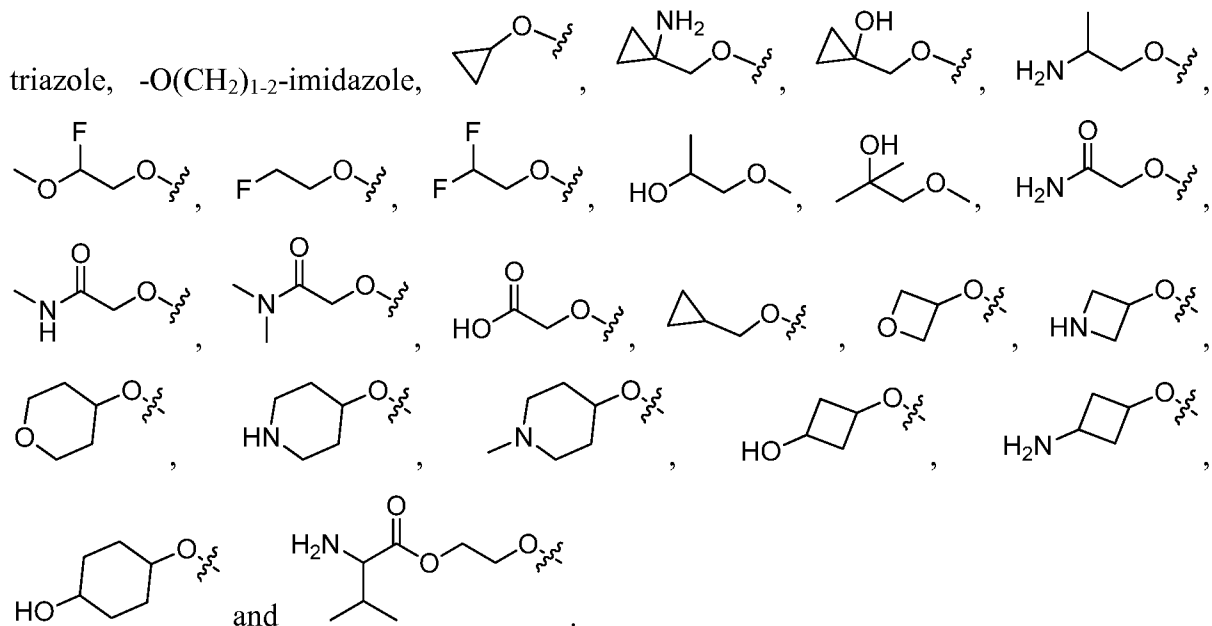


In some embodiments, A can be a substituted phenyl that is substituted with 3 more substituents. In other embodiments, A can be unsubstituted phenyl. In some embodiments, A can be an optionally substituted naphthyl.

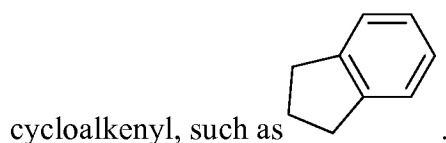
[0121] In some embodiments and without limitation, A can be a phenyl substituted with one or more substituents selected from an unsubstituted C_{1-4} alkyl, an optionally substituted C_{1-4} alkyl, cycloalkyl, hydroxy, an optionally substituted C_{1-4} alkoxy, C_{1-4} alkoxy, halogen, haloalkyl, an optionally substituted haloalkoxy, nitro, amino, mono-substituted amino, di-substituted amine, sulfenyl, alkyoxyalkyl, aryl, mono-cyclic heteroaryl, mono-cyclic 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, 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 C₁₋₄ alkyl.

[0122] 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, N,N-di-methyl-amine, N,N-di-ethyl-amine, N-methyl-N-ethyl-amine, N-methyl-amino, N-ethyl-amino, amino, alkylthio (such as CH₃CH₂S-), phenyl, imidazole, morpholinyl, pyrazole, pyrrolidinyl, pyridinyl, piperidinyl, pyrrolidinone, pyrimidine, pyrazine, 1,2,4-oxadiazole, -(CH₂)₁₋₂-NH(CH₃), -O(CH₂)₂-NH₂, -O(CH₂)₂-NH(CH₃), -O(CH₂)₂-N(CH₃)₂, -O-(CH₂)₂₋₄OH, -O(CH₂)₂OCH₃, -O(CH₂)₁₋₂-morpholinyl, -O(CH₂)₁₋₂-



[0123] 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

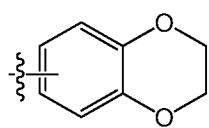


[0124] In some embodiments, A can be an optionally substituted aryl(C₁₋₂ alkyl). In some embodiments, A can be an optionally substituted benzyl.

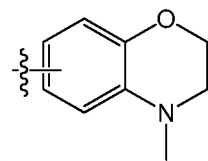
[0125] In some embodiments, A can be an optionally substituted mono-cyclic heteroaryl. In some embodiments, A can be an optionally substituted mono-cyclic 5-membered heteroaryl. In other embodiments, A can be an optionally substituted mono-cyclic 6-membered heteroaryl. In some embodiments, A can be an optionally substituted bi-cyclic heteroaryl.

[0126] 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 quinolone, an optionally substituted imidazole, an optionally substituted oxazole and an optionally substituted isoxazole. 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.

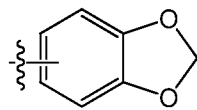
[0127] In some embodiments, A can be an optionally substituted heterocyclyl, for example, an optionally substituted mono-cyclic heterocyclyl or an optionally substituted bi-cyclic heterocyclyl. In some embodiments, A can be an optionally substituted



. In other embodiments, A can be an optionally substituted



In still other embodiments, A can be an optionally substituted



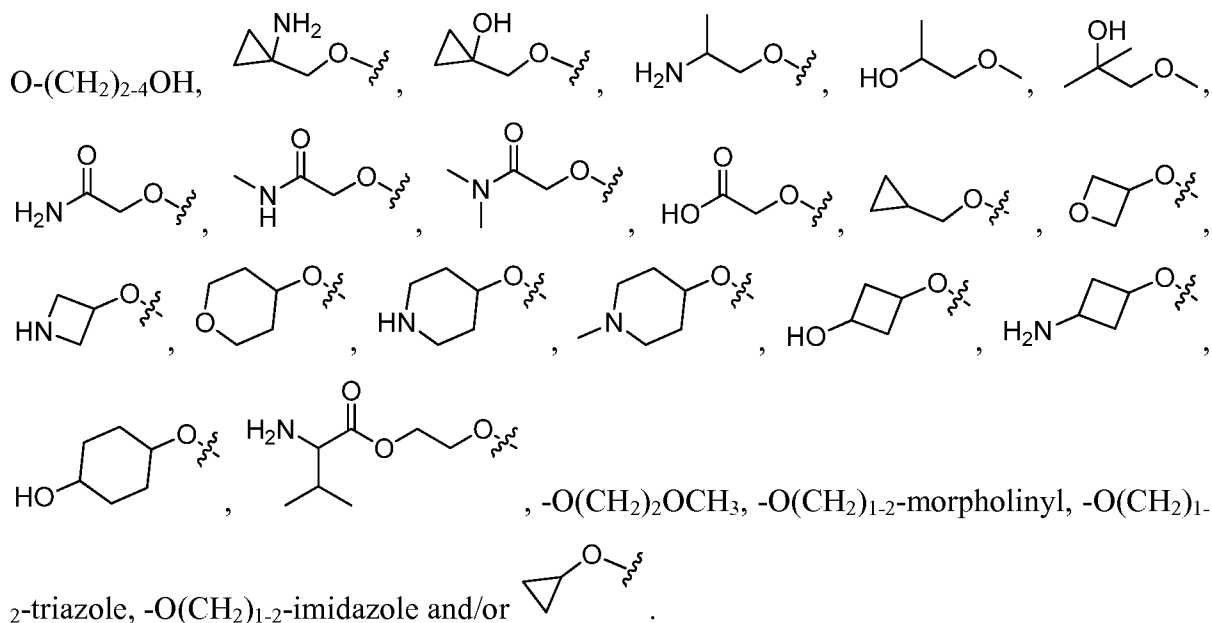
[0128] In some embodiments, A can be substituted with one or more R^A's. In some embodiments, one R^A can be present. In some embodiments, two R^A's can be present. In some embodiments, three R^A's can be present. In some embodiments, four or more R^A's can be present. When two or more R^A's are present, 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.

[0129] In some embodiments, R^A can be each independently selected from an unsubstituted C_{1-4} alkyl, an optionally substituted C_{1-4} alkyl, cycloalkyl, hydroxy, an optionally substituted C_{1-4} alkoxy, C_{1-4} alkoxy, halogen, haloalkyl, an optionally substituted haloalkoxy, nitro, amino, mono-substituted amino, di-substituted amine, sulfenyl, alkoxyalkyl, aryl, mono-cyclic heteroaryl, mono-cyclic 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, 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.

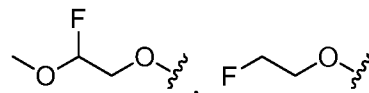
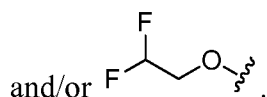
[0130] In some embodiments, each R^A can be an alkyl, such as methyl, ethyl, propyl (n-propyl and iso-propyl) and/or butyl (n-butyl, iso-butyl and t-butyl).

[0131] 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, $-O(CH_2)_2-NH_2$, $-O(CH_2)_2-NH(CH_3)$, $-O(CH_2)_2-N(CH_3)_2$, -



[0132] In some embodiments, each R^A can be haloalkyl, for example, trifluoromethyl.

[0133] In some embodiments, each R^A can be an optionally substituted haloalkoxy, for example, difluoromethoxy, trifluoromethoxy,



[0134] In some embodiments, each R^A can be halogen, for example, chloro, bromo and/or fluoro.

[0135] 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.

[0136] In some embodiments, each R^A can be hydroxy.

[0137] In some embodiments, each R^A can be alkylthio, for example ethylthio.

[0138] In some embodiments, each R^A can be aminoalkyl, such as $-(CH_2)_{1-2}-NH(CH_3)$.

[0139] In some embodiments, each R^A can be alkoxyalkyl, for example, $-CH_2-O-CH_3$.

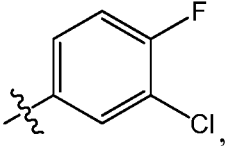
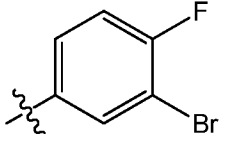
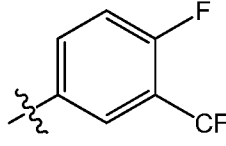
[0140] In some embodiments, each R^A can be aminoalkyl, for example, $-CH_2-NH_2$ and/or $-CH_2-N(CH_3)H$.

[0141] In some embodiments, each R^A can be an optionally substituted aryl, for example, an optionally substituted phenyl.

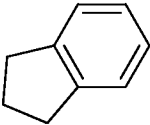
[0142] In some embodiments, each R^A can be an optionally substituted mono-cyclic heteroaryl, such as an optionally substituted imidazole, an optionally substituted pyrazole, an optionally substituted pyridinyl, an optionally substituted pyrimidine, an optionally substituted pyrazine and/or an optionally substituted 1,2,4-oxadiazole.

[0143] In some embodiments, each R^A can be an optionally substituted mono-cyclic heterocyclyl, for example, an optionally substituted pyrrolidinyl, an optionally substituted piperidinyl, an optionally substituted morpholinyl and/or an optionally substituted pyrrolidinone.

[0144] 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 di-substituted phenyl, for example a di-halo substituted phenyl. For example, di-halo substituted phenyls include, but are not

limited to, ,  and . 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.

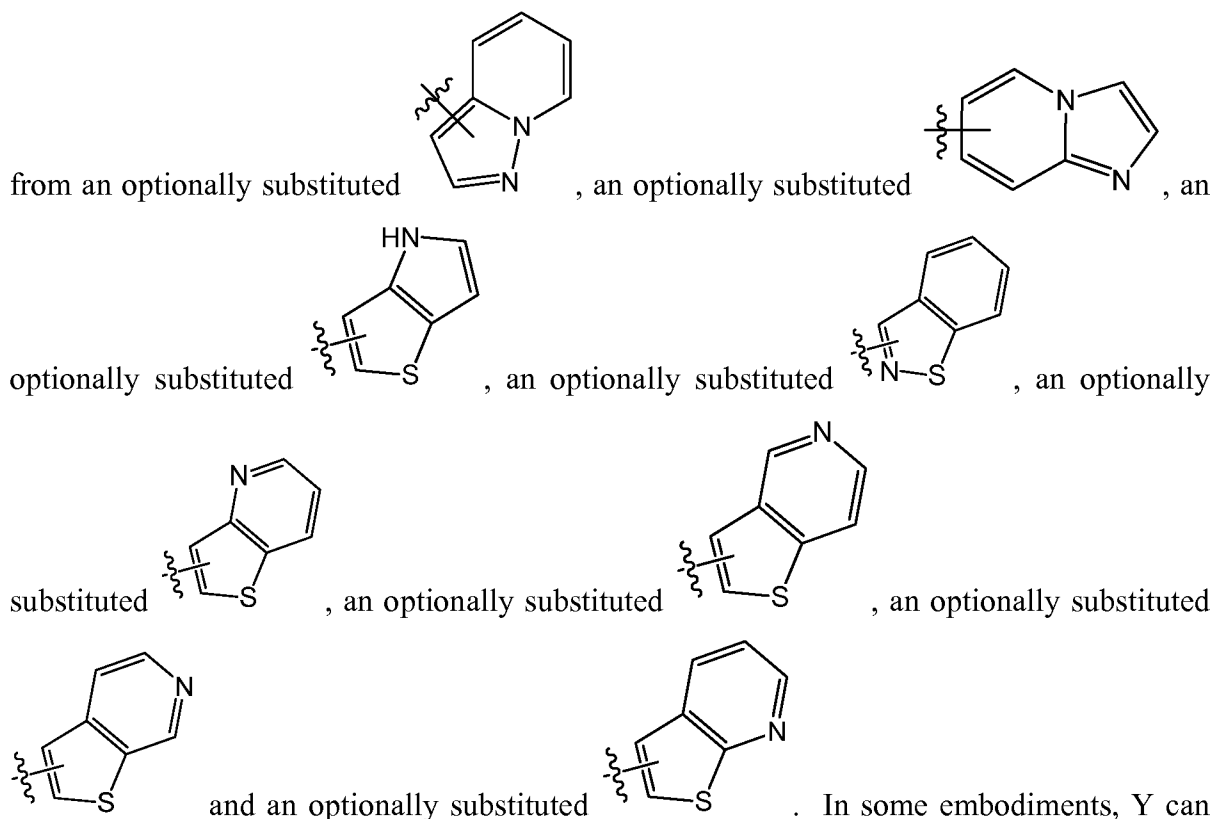
[0145] In some embodiments, Y can be an optionally substituted acylalkyl, such as an optionally substituted acyl(C₁₋₃ alkyl). In other embodiments, Y can be an optionally substituted cycloalkyl (e.g., an optionally substituted cyclohexyl and an optionally substituted cycloheptyl). In still other embodiments, Y can be an optionally substituted cycloalkenyl, for example, an optionally substituted cyclohexenyl. In other embodiments, Y

can be an optionally substituted bi-cyclic cycloalkenyl, such as .

[0146] 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.

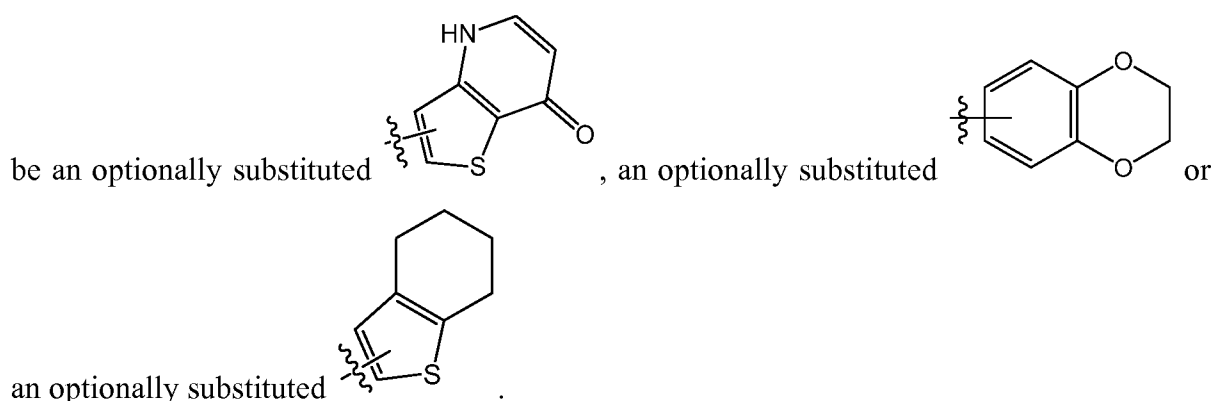
[0147] In some embodiments, Y can be an optionally substituted bi-cyclic heteroaryl. In some embodiments, Y can be selected from an optionally substituted benzothiophene, an optionally substituted benzofuran, an optionally substituted indole, an optionally substituted quinoline, an optionally substituted 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

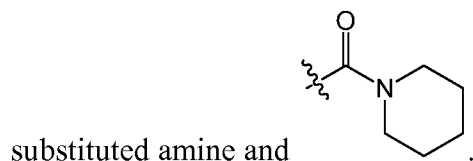


be a substituted bi-cyclic heteroaryl, including those described herein. In some embodiments, Y can be an unsubstituted bi-cyclic heteroaryl, including those described herein.

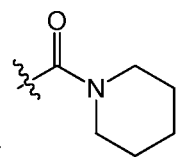
[0148] In some embodiments, Y can be an optionally substituted heterocyclyl. In some embodiments, Y can be an optionally substituted mono-cyclic heterocyclyl. In other embodiment, Y can be an optionally substituted bi-cyclic heterocyclyl. For example, Y can



[0149] 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-

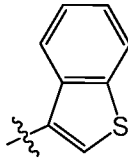


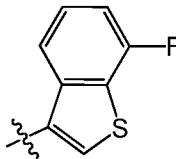
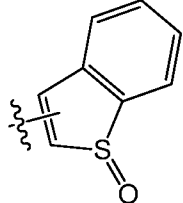
[0150] In some embodiments, when Y is an optionally substituted phenyl, the phenyl can be substituted 1, 2, 3 or more times with cyano, halogen, an optionally substituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an optionally substituted aryl, an optionally substituted 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}

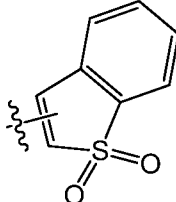
alkyl amine and/or . In other embodiments, when Y is an optionally substituted mono-cyclic heteroaryl, the mono-cyclic heteroaryl can be substituted 1, 2, 3 or more times with halo, an optionally substituted C_{1-4} alkyl, an optionally substituted phenyl and/or an unsubstituted acyl. In still other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

[0151] 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 .

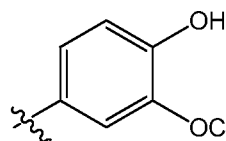
[0152] In some embodiments, Y can be an optionally substituted benzofuran.

[0153] 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.

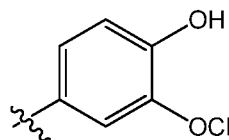
[0154] In some embodiments, Y can be substituted with one or more halogen. In some embodiments, Y can be substituted with one or more unsubstituted C_{1-4} alkyl. In some embodiments, Y can be substituted with more or more hydroxy. In some embodiments, Y can be substituted with one or more optionally substituted phenyl. In some embodiments, Y can be substituted with one or more alkoxy. In some embodiments, Y can be substituted

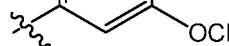
with one or more acyl. In some embodiments, Y can be substituted with one or more amino, mono-substituted amino, or di-substituted amino. In some embodiments, Y can be substituted with one or more haloalkyl. In some embodiments, Y can be substituted with one or more haloalkoxy. In some embodiments, Y can be substituted with one or more C-carboxy. In some embodiments, Y can be substituted with one or more C-amido.

[0155] In some embodiments, when X^1 is NR^{3a1} , $X^2-----X^3$ is $N=CR^4$, Y is an optionally substituted indolyl, then R^4 is selected from hydrogen, cyano, an optionally substituted C_{2-6} alkyl, an optionally substituted acylalkyl, an optionally substituted hydroxyalkyl, an optionally substituted alkoxy(alkyl), an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, haloalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkyl(C_{1-6} alkyl), an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments, when X^1 is NR^{3a1} , $X^2-----X^3$ is $N=CR^4$, Y is



then R^4 is selected from cyano, halo(C_{1-8} alkyl), an optionally substituted acylalkyl, an optionally substituted C_{1-8} alkyl, an optionally substituted hydroxyalkyl, an optionally substituted alkoxy(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 C_{3-6} cycloalkyl(C_{1-6} alkyl), an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments, Y cannot be an optionally substituted indolyl. In other



embodiments, Y cannot be . In some embodiments, R^4 cannot be methyl. In other embodiments, R^4 cannot be hydrogen.

[0156] In some embodiments, the compound of Formula (I) can be selected from the following compounds: 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130,

131, 132, 133, 134, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 242, 244, 245, 246A, 246B, 247, 300, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 415, 416, 417, 419, 422, 423, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 437, 438, 439, 440, 441, 442, 443, 444, 445, 448A, 448B, 449, 450, 453, 454, 455A, 455B, 456, 457, 458A, 458B, 459, 460, 461, 462A, 462B, 463A, 463B, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 400-1, 400-2, 400-3, 400-4, 400-5, 400-6, 400-7, 400-8, 400-9, 400-10, 400-11, 400-12, 400-13, 400-14, 400-15, 400-16, 400-17, 400-18, 400-19, 400-20, 400-21, 400-22, 400-24, 400-25, 400-26, 400-27, 400-28, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514A, 514B, 600, 601, 602, 603A, 603B, 604, 605, 606, 650, 651, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 901, 1206, 1352, 2300, 2301, 2302, 2303, 2304, 2400, 2401, 4105, 4304, 4305, 4306, 4307, 4308, 4309, 4310, 4311, 4312, 4313 and 4314.

[0157] In some embodiments, the compound of Formula (I) can be selected from the following compounds: 1200, 1202, 1204, 1209, 1211, 1213, 1214, 1216, 1217, 1220, 1221, 1223, 1224, 1225, 1226, 1227, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1255, 1256, 1257, 1258, 1300, 1301, 1302, 1303, 1304, 1307, 1308, 1309, 1310, 1311, 1312, 1313, 1314, 1315, 1316, 1317, 1318, 1319, 1320, 1321, 1322, 1323, 1325, 1326, 1327, 1328, 1329, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1340, 1341, 1343, 1344, 1345, 1346, 1359, 1360, 1401, 1402, 1403, 1404, 1405, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1517, 1518, 1519, 1520, 1521, 1522, 1523, 1524, 1525, 1526, 1527, 1528, 1529, 1530, 1531, 1532, 1533, 1534, 1535, 1536, 1537, 1538, 1539, 1540, 1541, 1601, 1602, 1603, 1604, 1605, 1606, 1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1619, 1620, 1621, 1622, 1623, 1800, 1802, 1803, 1804, 1805, 1806, 1807, 1808, 1809, 1810, 1811, 1812, 1813, 1814, 1815, 1816, 1817, 1818, 1819, 1820, 1821, 1822, 1823, 1824, 1825, 1826, 1829, 1830, 1831, 1832, 1833, 1834, 1835, 1836, 1837, 1838, 1839, 1900, 1901, 1902, 1903, 2000, 2100, 2101, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2111, 2112, 2113, 2114, 2115, 2504, 2506, 2507, 2508, , 2601, 2602, 2603, 2604, 2605, 2613, 2615, 2617, 2618, 2619, 2620, 2621, 2622, 2624, 2626, 2627, 2638, 2641, 2642, 2643, 2644,

2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2654, 3302, 3800, 3903, 4002, 4201, 4202, 4203, 4204, 4205, 4206, 4207, 4208, 4209, 4210, 4212 and 4216.

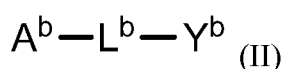
[0158] In some embodiments, the compound of Formula (I) can be selected from the following compounds: 840, 1100, 1101, 1201, 1205, 1210, 1215, 1219, 1222, 1228, 1240, 1241, 2204, 2205, 2800, 2801, 3200, 3401, 3500, 3501, 3900 and 4303.

[0159] In some embodiments, the compound of Formula (I) can be selected from the following compounds: 900, 902, 903, 904, 908, 910, 917, 1000, 2803, 3300 and 4302.

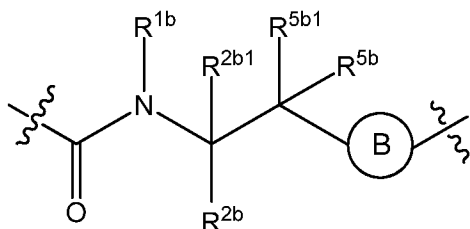
[0160] In some embodiments, the compound of Formula (I) can be selected from the following compounds: 239, 240, 241, 2305, 2306 and 2802.

Formula (II)

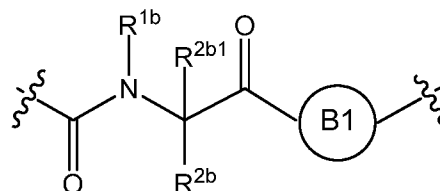
[0161] Some embodiments disclosed herein relate to a compound of Formula (II), or a pharmaceutically acceptable salt thereof, having the structure:



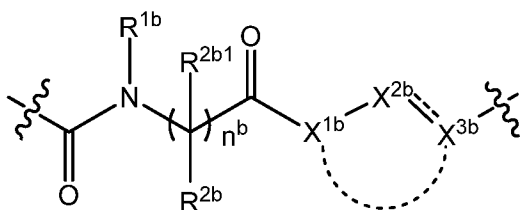
wherein: L^b can be selected from:



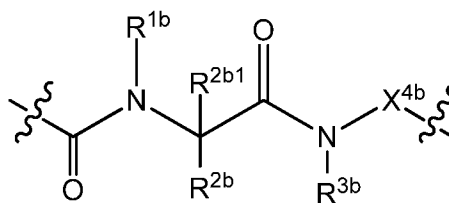
(IIa),



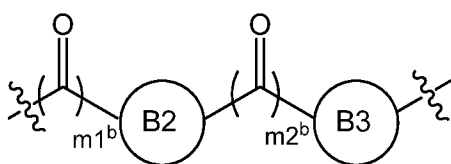
(IIb),



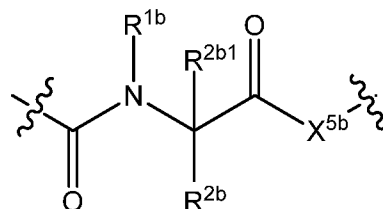
(IIc),



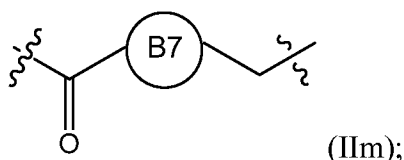
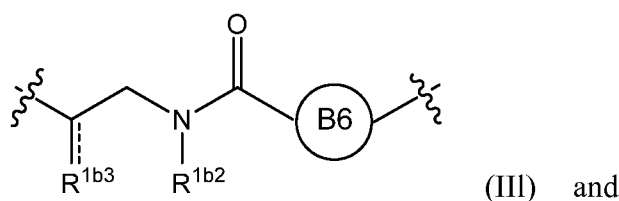
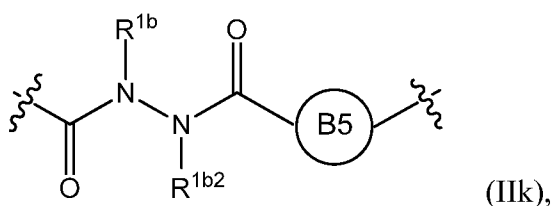
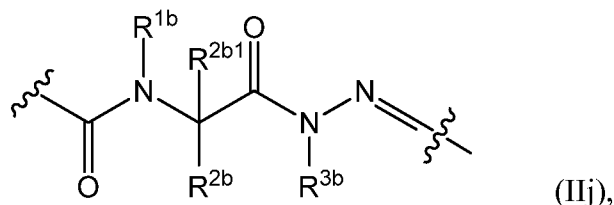
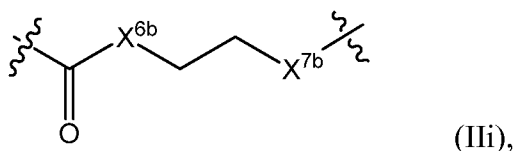
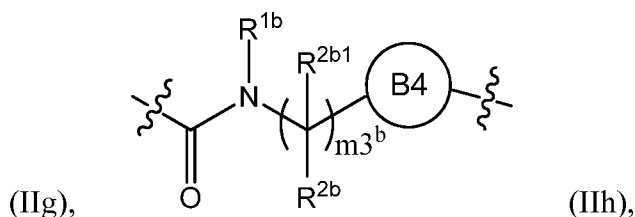
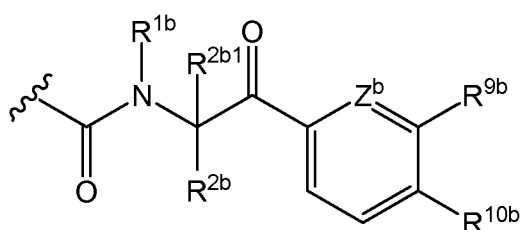
(IIe),



(IIe),

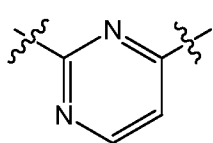


(IIe),

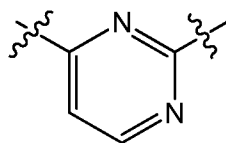


A^b can be an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-2} alkyl), an optionally substituted heteroaryl or an optionally substituted heterocyclyl. Y^b can be an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; when L^b is Formula (IIc), ----- between X^{2b} and X^{3b} represents a single or double bond between X^{2b} and X^{3b} , when ----- between X^{2b} and X^{3b} is a double bond, then X^{1b} can be independently NR^{3b} or $CR^{3b1}R^{3b2}$, X^{2b} can be N (nitrogen) or CR^{7b1} , and X^{3b} can be N (nitrogen) or CR^{4b} ; when ----- between X^{2b} and X^{3b} is a single bond, then X^{1b} can be independently NR^{3b} or $CR^{3b1}R^{3b2}$, X^{2b} can be O (oxygen), NR^{7b} or $C(R^{7b2})(R^{7b3})$, and X^{3b} can be NR^{4b} , $C(=O)$ or $CR^{4b}R^{8b}$; or X^{1b} , X^{2b} and X^{3b} 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^{1b} and X^{3b} together; with the proviso that the valencies of X^{1b} , X^{2b} and X^{3b} are 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; X^{4b} can be NR^{6b1} or $C(R^{6b2})_2$; X^{5b} can be NR^{6b3} or $C(R^{6b4})_2$; X^{6b} can be NR^{6b5} or $C(=O)$; X^{7b} can be $NR^{6b6}CH_2$ or $-C(=O)-$ an optionally substituted pyridinyl-; Z^b can be N or CH; R^{1b} can be hydrogen or an unsubstituted C_{1-4} alkyl; R^{1b2} can be hydrogen or an unsubstituted C_{1-4} alkyl; when L^b is Formula (IIg), then Y^b is absent; when ----- of Formula (III) is a single bond, then R^{1b3} can be hydroxy; when ----- of Formula (III) is a double bond, then R^{1b3} can be O (oxygen); R^{2b} and R^{2b1} can be each independently hydrogen or an optionally substituted C_{1-4} alkyl, and when more than one R^{2b} and/or more than one R^{2b1} are present, each R^{2b} and each R^{2b1} can be the same or different; R^{3b} , R^{3b1} and R^{3b2} can be hydrogen or an unsubstituted C_{1-4} alkyl; R^{4b} can be hydrogen, an optionally substituted C_{1-4} alkyl or an optionally substituted alkoxyalkyl; R^{5b} and R^{5b1} can be each independently hydrogen or hydroxy; R^{6b1} , each R^{6b2} , R^{6b3} , each R^{6b4} , R^{6b5} and R^{6b6} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{7b} and R^{7b1} can be each independently be hydrogen or an unsubstituted C_{1-4} alkyl; R^{7b2} and R^{7b3} can be each independently hydrogen or an unsubstituted C_{1-4} alkyl; or R^{7b2} and R^{7b3} together form $=O$; R^{8b} can be hydrogen or an unsubstituted C_{1-4} alkyl; R^{9b} and R^{10b} can be each independently an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} alkenyl or an unsubstituted C_{1-4} alkoxy; or R^{9b} and R^{10b} can be taken together to form an unsubstituted aryl, an unsubstituted heteroaryl or an optionally substituted heterocyclyl; ring B is an optionally substituted



or an optionally substituted

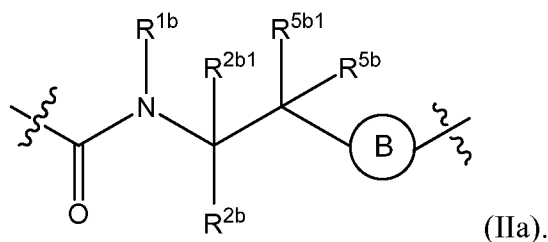


; ring B1 can be an optionally

substituted mono-cyclic cycloalkyl, an optionally substituted phenyl, an optionally substituted mono-cyclic heteroaryl or an optionally substituted mono-cyclic heterocyclyl; ring B2 can be an optionally substituted heteroaryl; ring B3 can be an optionally substituted pyridinyl; ring B4 can be an optionally substituted heteroaryl or an optionally substituted heterocyclyl; ring B5 can be an optionally substituted pyridinyl; ring B6 can be an optionally substituted pyridinyl; ring B7 can be an optionally substituted heterocyclyl; $m1^b$ and $m2^b$ can be each independently 0 or 1; provided that at least one of $m1^b$ and $m2^b$ is 1; $m3^b$ can be 0 or 1; and n^b can be 2 or 3.

Formula (IIa)

[0162] In some embodiments, L^b can be Formula (IIa):

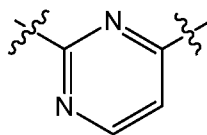


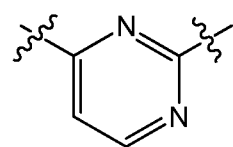
[0163] In some embodiments of Formula (IIa), R^{1b} can be hydrogen. In other embodiments of Formula (IIa), R^{1b} can be an unsubstituted C_{1-4} alkyl.

[0164] In some embodiments of Formula (IIa), R^{2b} and R^{2b1} both can be hydrogen. In other embodiments of Formula (IIa), one of R^{2b} and R^{2b1} can be hydrogen and the other of R^{2b} and R^{2b1} can be an optionally substituted C_{1-4} alkyl. In still other embodiments of Formula (IIa), R^{2b} and R^{2b1} both can be an optionally substituted C_{1-4} alkyl.

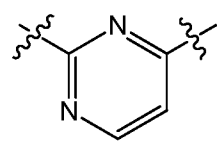
[0165] In some embodiments of Formula (IIa), both R^{5b} and R^{5b1} can be hydrogen. In other embodiments, R^{5b} can be hydrogen, and R^{5b1} can be hydroxy.

[0166] In some embodiments of Formula (IIa), ring B can be an optionally

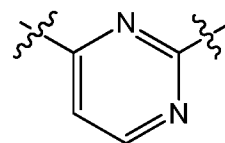
substituted . In other embodiments, ring B can be an optionally substituted



. In some embodiments of Formula (IIa), ring B can be an unsubstituted



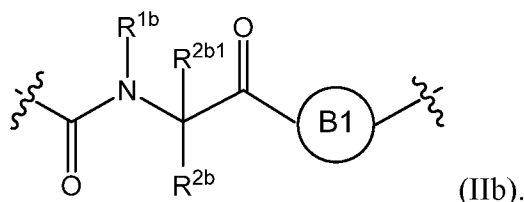
. In other embodiments, ring B can be an unsubstituted



[0167] In some embodiments, a compound of Formula (II) with L^b being (IIa) can be selected from the following compounds: 839, 1207 and 1208.

Formula (IIb)

[0168] In some embodiments, L^b can be Formula (IIb):

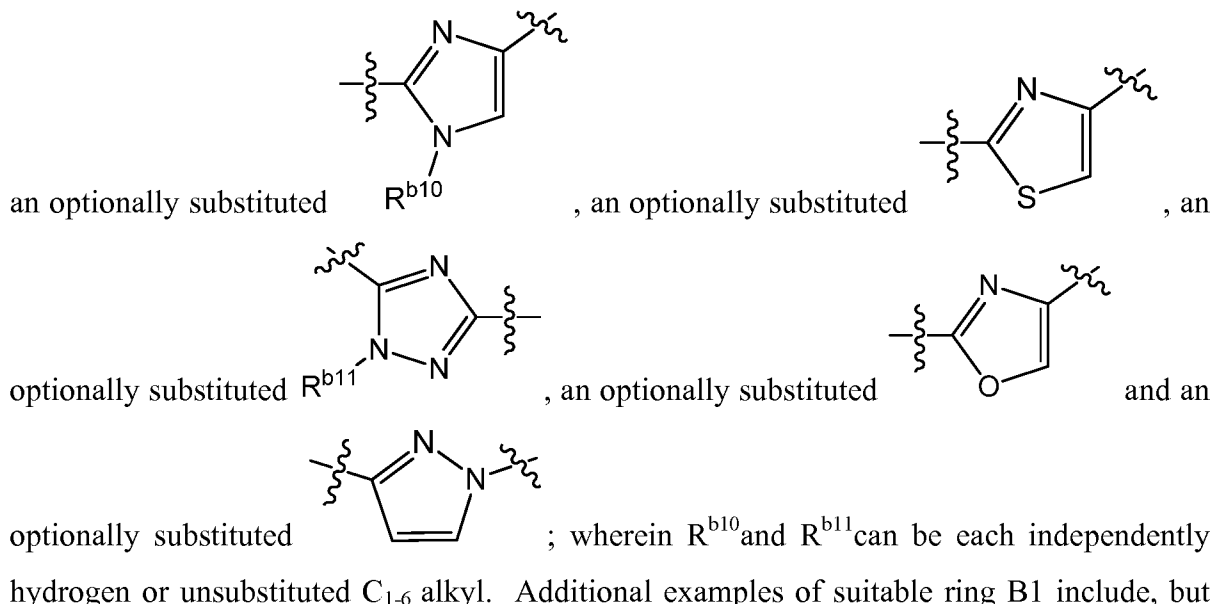


[0169] In some embodiments of Formula (IIb), R^{1b} can be hydrogen. In other embodiments of Formula (IIb), R^{1b} can be an unsubstituted C_{1-4} alkyl.

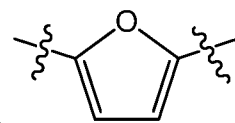
[0170] In some embodiments of Formula (IIb), R^{2b} and R^{2b1} both can be hydrogen. In other embodiments of Formula (IIb), one of R^{2b} and R^{2b1} can be hydrogen and the other of R^{2b} and R^{2b1} can be an optionally substituted C_{1-4} alkyl. In still other embodiments of Formula (IIb), R^{2b} and R^{2b1} both can be an optionally substituted C_{1-4} alkyl.

[0171] In some embodiments of Formula (IIb), ring B1 can be an optionally substituted mono-cyclic cycloalkyl. In other embodiments of Formula (IIb), ring B1 can be an optionally substituted phenyl. In still other embodiments of Formula (IIb), ring B1 can be an optionally substituted mono-cyclic heteroaryl. In yet still other embodiments of Formula (IIb), ring B1 can be or an optionally substituted mono-cyclic heterocyclyl.

[0172] Examples of suitable ring B1 include, but are not limited to, the following:

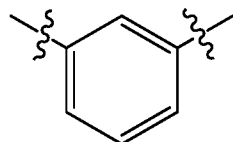


are not limited to, the following: an optionally substituted

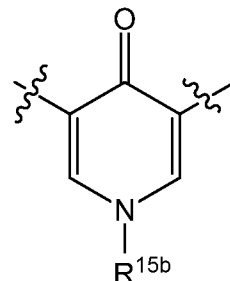


, an optionally

substituted

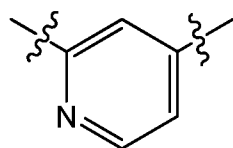


, an optionally substituted

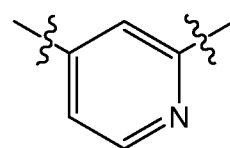


, an optionally

substituted

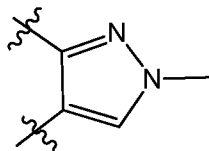


, an optionally substituted

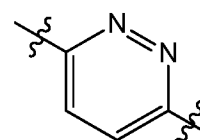


, an optionally

substituted



and an optionally substituted



; wherein R^{15b} can

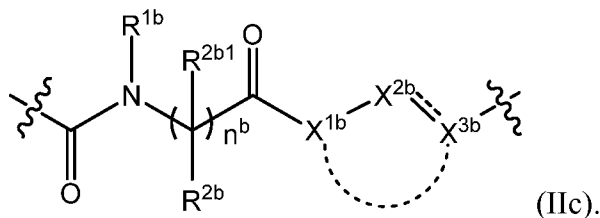
be hydrogen or an unsubstituted C₁₋₄ alkyl.

[0173] In some embodiment, a compound of Formula (II) with L^b being (IIb) can be selected from the following compounds: 860, 1206, 1352, 1353, 1354, 1355, 1356, 1358, 2203, 2500, 2502, 2607 and 3201.

[0174] In other embodiment, a compound of Formula (II) with L^b being (IIb) can be selected from the following compounds: 1218, 1337, 1338, 1351, 2102, 2200, 2606, 2623, 2653 and 3901.

Formula (IIc)

[0175] In some embodiments, L^b can be Formula (IIc):

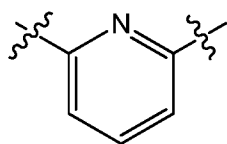


[0176] In some embodiments of Formula (IIc), R^{1b} can be hydrogen. In other embodiments of Formula (IIc), R^{1b} can be an unsubstituted C₁₋₄ alkyl.

[0177] In some embodiments of Formula (IIc), n^b can be 2. In other embodiments of Formula (IIc), n^b can be 3.

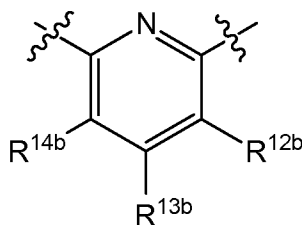
[0178] In some embodiments of Formula (IIc), each R^{2b} and each R^{2b1} can be hydrogen. In other embodiments of Formula (IIc), one or more R^{2b} 's can be hydrogen and one or more R^{2b1} 's can be an optionally substituted C_{1-4} alkyl. In some embodiments of Formula (IIc), each R^{2b} and each R^{2b1} can be an optionally substituted C_{1-4} alkyl.

[0179] In some embodiments of Formula (IIc), X^{1b} can be NR^{3b} or $CR^{3b1}R^{3b2}$; ---- between X^{2b} and X^{3b} can be a double bond, X^{2b} can be N (nitrogen) or CR^{7b1} , and X^{3b} can be N (nitrogen) or CR^{4b} . In other embodiments of Formula (IIc), X^{1b} can be NR^{3b} or $CR^{3b1}R^{3b2}$; ----- between X^{2b} and X^{3b} can be a single bond, X^{2b} can be O (oxygen), NR^{7b} or $C(R^{7b2})(R^{7b3})$, and X^{3b} can be NR^{4b} , $C(=O)$ or $CR^{4b}R^{8b}$. In still other embodiments of Formula (IIc), X^{1b} , X^{2b} and X^{3b} 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^{1b} and X^{3b} together; 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 such that X^{1b} , X^{2b} and X^{3b} are uncharged. In some embodiments of Formula (IIc), X^{1b} can be NR^{3b} , ----- between X^{2b} and X^{3b} can be a double bond, X^{2b} can be N (nitrogen), and X^{3b} can be CR^{4b} (such as CH or $C(CH_3)$). In other embodiments of Formula (IIc), X^{1b} and X^{3b} can be each C (carbon) and X^{2b} can be N (nitrogen). In some embodiments, X^{1b} , X^{2b} and X^{3b} can form an optionally substituted heteroaryl, for example, an



optionally substituted

. In some embodiments, the optionally substituted



pyridinyl can have the structure

, wherein R^{12b} , R^{13b} and R^{14b} can be

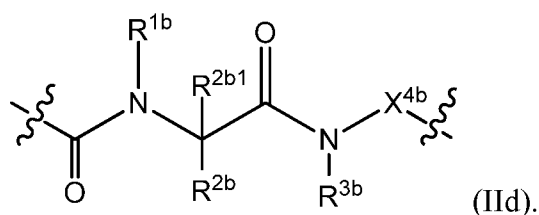
each independently selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an

optionally substituted C₃₋₆ cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C₁₋₈ alkyl), haloalkyl and an optionally substituted C-carboxy; or R^{12b} and R^{13b} along with the atoms to which they are connected can be taken together to form an optionally substituted cycloalkyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{14b} can be selected from hydrogen, halogen, hydroxy, an optionally substituted C₁₋₈ alkyl, an optionally substituted C₂₋₈ alkenyl, an optionally substituted C₂₋₈ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C₁₋₈ alkyl), haloalkyl and an optionally substituted C-carboxy. 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 C₁₋₄ alkyl. In some embodiments, the valencies of X^{1b}, X^{2b} and X^{3b} can be each independently satisfied hydrogen or methyl.

[0180] In some embodiment, a compound of Formula (II) with L^b being (IIc) can be selected from the following compounds: 243 and 1801.

Formula (IId)

[0181] In some embodiments, L^b can be Formula (IId):



[0182] In some embodiments of Formula (IId), R^{1b} can be hydrogen. In other embodiments of Formula (IId), R^{1b} can be an unsubstituted C₁₋₄ alkyl.

[0183] In some embodiments of Formula (IId), R^{2b} and R^{2b1} both can be hydrogen. In other embodiments of Formula (IId), one of R^{2b} and R^{2b1} can be hydrogen and

the other of R^{2b} and R^{2b1} can be an optionally substituted C_{1-4} alkyl. In still other embodiments of Formula (IId), R^{2b} and R^{2b1} both can be an optionally substituted C_{1-4} alkyl.

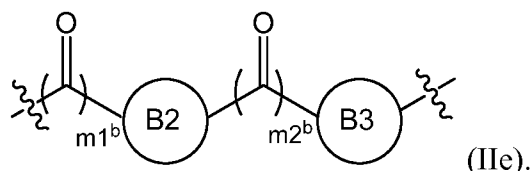
[0184] In some embodiments of Formula (IId), R^{3b} can be hydrogen. In other embodiments, R^{3b} can be an unsubstituted C_{1-4} alkyl.

[0185] In some embodiments of Formula (IId), X^{4b} can be NR^{6b1} , for example, NH. In some of Formula (IId), X^{4b} can be $C(R^{6b2})_2$, such as CH_2 .

[0186] In some embodiment, a compound of Formula (II) with L^b being (IId) can be compound 4301.

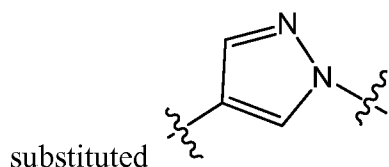
Formula (IIe)

[0187] In some embodiments, L^b can be Formula (IIe):

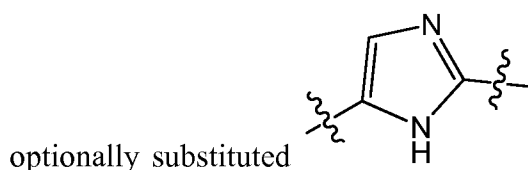


[0188] In some embodiments of Formula (IIe), $m1^b$ can be 0, and $m2^b$ can be 1. In other embodiments of Formula (IIe), $m1^b$ can be 1, and $m2^b$ can be 0. In still other embodiments of Formula (IIe), $m1^b$ can be 1, and $m2^b$ can be 1.

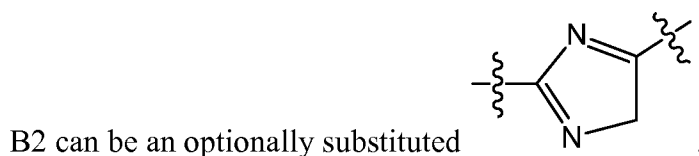
[0189] In some embodiments of Formula (IIe), ring B2 can be an optionally



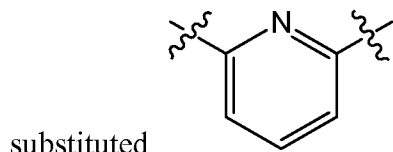
. In other embodiments of Formula (IIe), ring B2 can be an



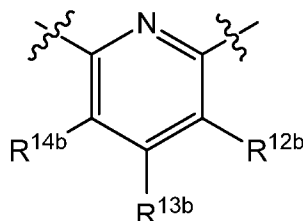
. In still other embodiments of Formula (IIe), ring



[0190] In some embodiments of Formula (IIe), ring B3 can be an optionally



. In some embodiments, the optionally substituted pyridinyl

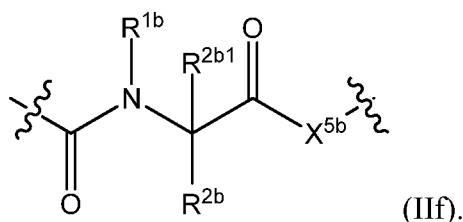


can have the structure , wherein R^{12b} , R^{13b} and R^{14b} can be each independently selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl, 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 and an optionally substituted C-carboxy; or R^{12b} and R^{13b} along with the atoms to which they are connected can be taken together to form an optionally substituted cycloalkyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{14b} 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.

[0191] In some embodiments, a compound of Formula (II) with L^b being (IIe) can be selected from the following compounds: 1702, 1703 and 2612.

Formula (IIf)

[0192] In some embodiments, L^b can be Formula (IIf):



[0193] In some embodiments of Formula (IIf), R^{1b} can be hydrogen. In other embodiments of Formula (IIf), R^{1b} can be an unsubstituted C_{1-4} alkyl.

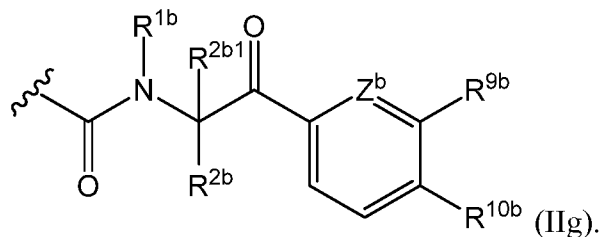
[0194] In some embodiments of Formula (IIf), R^{2b} and R^{2b1} both can be hydrogen. In other embodiments of Formula (IIf), one of R^{2b} and R^{2b1} can be hydrogen and the other of R^{2b} and R^{2b1} can be an optionally substituted C_{1-4} alkyl. In still other embodiments of Formula (IIf), R^{2b} and R^{2b1} both can be an optionally substituted C_{1-4} alkyl.

[0195] In some embodiments of Formula (IIf), X^{5b} can be NR^{6b3} , such as NH or $N(CH_3)$. In other embodiments of Formula (IIf), X^{5b} can be $C(R^{6b4})_2$, for example, CH_2 or $C(CH_3)_2$.

[0196] In some embodiment, a compound of Formula (II) with L^b being (IIf) can be selected from the following compounds: 905, 906, 907, 909, 911, 912, 913, 914, 915, 916, 4100 and 4104.

Formula (IIg)

[0197] In some embodiments, L^b can be Formula (IIg):



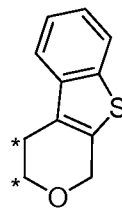
[0198] In some embodiments of Formula (IIg), R^{1b} can be hydrogen. In other embodiments of Formula (IIg), R^{1b} can be an unsubstituted C_{1-4} alkyl.

[0199] In some embodiments of Formula (IIg), R^{2b} and R^{2b1} both can be hydrogen. In other embodiments of Formula (IIg), one of R^{2b} and R^{2b1} can be hydrogen and

the other of R^{2b} and R^{2b1} can be an optionally substituted C_{1-4} alkyl. In still other embodiments of Formula (IIg), R^{2b} and R^{2b1} both can be an optionally substituted C_{1-4} alkyl.

[0200] In some embodiments of Formula (IIg), Z^b can be N (nitrogen). In some embodiments of Formula (IIg), Z^b can be CH.

[0201] In some embodiments of Formula (IIg), one of R^{9b} and R^{10b} can be an unsubstituted C_{1-4} alkyl and the other of R^{9b} and R^{10b} can be an unsubstituted C_{1-4} alkoxy. In other embodiments of Formula (IIg), one of R^{9b} and R^{10b} can be an unsubstituted C_{1-4} alkenyl and the other of R^{9b} and R^{10b} can be an unsubstituted C_{1-4} alkoxy. In still other embodiments of Formula (IIg), R^{9b} and R^{10b} can be taken together to form an unsubstituted aryl (for example, phenyl). In some embodiments of Formula (IIg), R^{9b} and R^{10b} can be taken together to form an unsubstituted heteroaryl, such as piperdinyl. In other embodiments of Formula (IIg), R^{9b} and R^{10b} can be taken together to form an optionally substituted

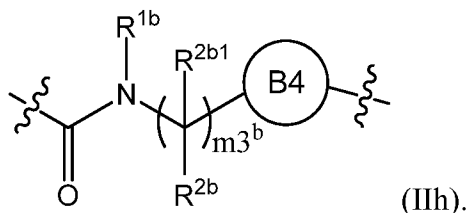


heterocyclyl, for example, an optionally substituted, wherein * each indicate a point of attachment to the 6-membered ring.

[0202] In some embodiments, a compound of Formula (II) with L^b being (IIg) can be selected from the following compounds: 1700, 1701, 2614, 2616, 2701 and 2703.

Formula (IIh)

[0203] In some embodiments, L^b can be Formula (IIh):



[0204] In some embodiments of Formula (IIh), R^{1b} can be hydrogen. In other embodiments of Formula (IIh), R^{1b} can be an unsubstituted C_{1-4} alkyl.

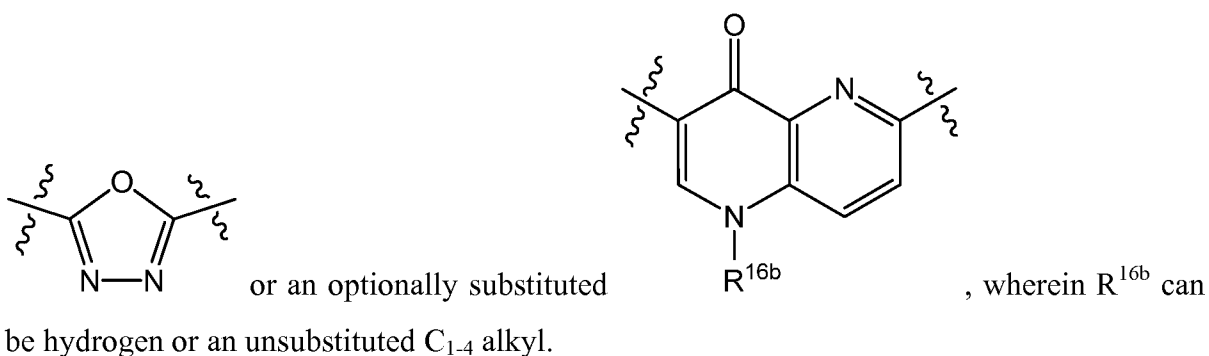
[0205] In some embodiments of Formula (IIh), R^{2b} and R^{2b1} both can be hydrogen. In other embodiments of Formula (IIh), one of R^{2b} and R^{2b1} can be hydrogen and

the other of R^{2b} and R^{2b1} can be an optionally substituted C_{1-4} alkyl. In still other embodiments of Formula (IIh), R^{2b} and R^{2b1} both can be an optionally substituted C_{1-4} alkyl.

[0206] In some embodiments of Formula (IIh), $m3^b$ can be 0. In other embodiments of Formula (IIh), $m3^b$ can be 1.

[0207] In some embodiments of Formula (IIh), ring B4 can be an optionally substituted heteroaryl. In other embodiments of Formula (IIh), ring B4 can be an optionally substituted heterocyclyl.

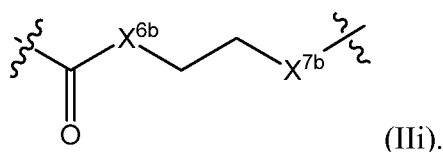
[0208] In some embodiments, ring B4 can be an optionally substituted



[0209] In some embodiments, a compound of Formula (II) with L^b being (IIh) can be selected from the following compounds: 2900, 2901 and 4103.

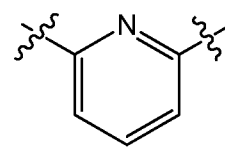
Formula (IIi)

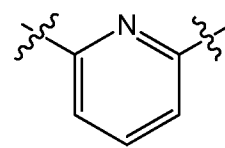
[0210] In some embodiments, L^b can be Formula (IIi):

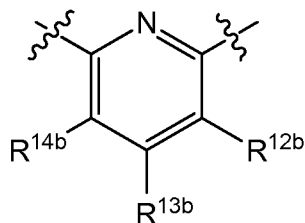


[0211] In some embodiments of Formula (IIi), X^{6b} can be NR^{6b5} and X^{7b} can be $NR^{6b6}CH_2$. In some embodiments, R^{6b5} and R^{6b6} can be both hydrogen. In other embodiments of Formula (IIi), R^{6b5} can be an unsubstituted C_{1-4} alkyl, and R^{6b6} can be hydrogen. In still other embodiments of Formula (IIi), R^{6b5} can be an unsubstituted C_{1-4} alkyl, and R^{6b6} can be hydrogen. In yet still other embodiments of Formula (IIi), R^{6b5} and R^{6b6} can be both an unsubstituted C_{1-4} alkyl.

[0212] In some embodiments of Formula (IIi), X^{6b} can be $C(=O)$ and X^{7b} can be $-C(=O)-$ an optionally substituted pyridinyl-. In some embodiments of Formula (IIi), the



optionally substituted pyridinyl of X^{7b} can be an optionally substituted . In some embodiments, the optionally substituted pyridinyl can have the structure

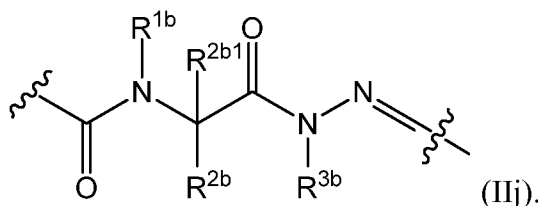


, wherein R^{12b} , R^{13b} and R^{14b} can be each independently selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted 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 and an optionally substituted C-carboxy; or R^{12b} and R^{13b} along with the atoms to which they are connected can be taken together to form an optionally substituted cycloalkyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{14b} 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.

[0213] In some embodiments, a compound of Formula (II) with L^b being (Iii) can be selected from the following compounds: 1339 and 4101.

Formula (IIj)

[0214] In some embodiments, L^b can be Formula (IIj):



[0215] In some embodiments of Formula (IIj), R^{1b} can be hydrogen. In other embodiments of Formula (IIj), R^{1b} can be an unsubstituted C_{1-4} alkyl.

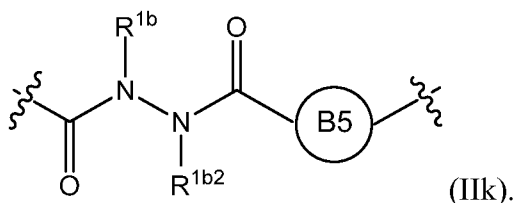
[0216] In some embodiments of Formula (IIj), R^{2b} and R^{2b1} both can be hydrogen. In other embodiments of Formula (IIj), one of R^{2b} and R^{2b1} can be hydrogen and the other of R^{2b} and R^{2b1} can be an optionally substituted C_{1-4} alkyl. In still other embodiments of Formula (IIj), R^{2b} and R^{2b1} both can be an optionally substituted C_{1-4} alkyl.

[0217] In some embodiments of Formula (IIj), R^{3b} can be hydrogen. In other embodiments of Formula (IIj), R^{3b} can be an unsubstituted C_{1-4} alkyl.

[0218] In some embodiments, a compound of Formula (II) with L^b being (IIj) can be selected from the following compounds: 414, 418, 420, 421, 424, 425, 426, 446, 447, 451, 452, 464 and 400-23.

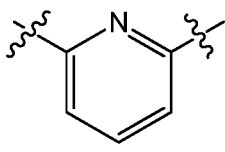
Formula (IIk)

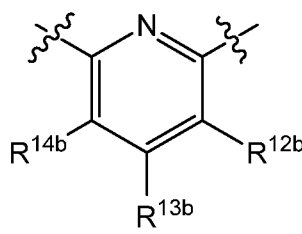
[0219] In some embodiments, L^b can be Formula (IIk):



[0220] In some embodiments of Formula (IIk), R^{1b} and R^{1b2} can be both hydrogen. In other embodiments of Formula (IIk), R^{1b} can be an unsubstituted C_{1-4} alkyl, and R^{1b2} can be hydrogen. In still other embodiments of Formula (IIk), R^{1b} can be an unsubstituted C_{1-4} alkyl, and R^{1b2} can be hydrogen. In yet still other embodiments of Formula (IIk), R^{1b} and R^{1b2} can be both an unsubstituted C_{1-4} alkyl.

[0221] In some embodiments of Formula (IIk), ring B5 can be an optionally

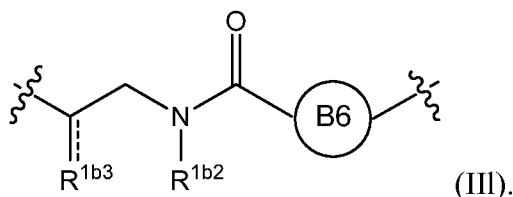
substituted optionally substituted . In some embodiments, the optionally

substituted pyridinyl can have the structure , wherein R^{12b}, R^{13b} and R^{14b} can be each independently selected from hydrogen, halogen, hydroxy, an optionally substituted C₁₋₈ alkyl, an optionally substituted C₂₋₈ alkenyl, an optionally substituted C₂₋₈ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C₁₋₈ alkyl), haloalkyl and an optionally substituted C-carboxy; or R^{12b} and R^{13b} along with the atoms to which they are connected can be taken together to form an optionally substituted cycloalkyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{14b} can be selected from hydrogen, halogen, hydroxy, an optionally substituted C₁₋₈ alkyl, an optionally substituted C₂₋₈ alkenyl, an optionally substituted C₂₋₈ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C₁₋₈ alkyl), haloalkyl and an optionally substituted C-carboxy.

[0222] In some embodiments, a compound of Formula (II) with L^b being (IIk) can be selected from the following compounds: 3100, 3101, 3102 and 3103.

Formula (III)

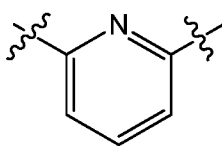
[0223] In some embodiments, L^b can be Formula (III):

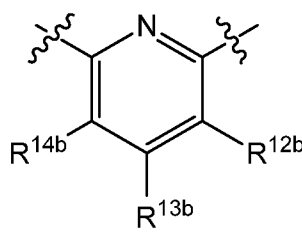


[0224] In some embodiments of Formula (III), R^{1b2} can be hydrogen. In other embodiments of Formula (III), R^{1b2} can be an unsubstituted C_{1-4} alkyl.

[0225] In some embodiments of Formula (III), ----- is a single bond, and R^{1b3} can be hydroxy. In other embodiments of Formula (III), ----- is a double bond, and R^{1b3} can be O (oxygen).

[0226] In some embodiments of Formula (III), ring B6 can be an optionally

substituted optionally substituted . In some embodiments, the optionally

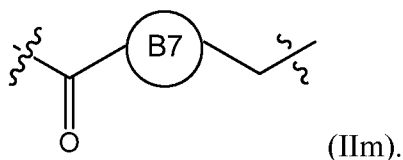
substituted pyridinyl can have the structure , wherein R^{12b} , R^{13b} and R^{14b} can be each independently selected from hydrogen, halogen, hydroxy, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted 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 and an optionally substituted C-carboxy; or R^{12b} and R^{13b} along with the atoms to which they are connected can be taken together to form an optionally substituted cycloalkyl an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl; and R^{14b} 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 C₃₋₆ cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, amino, mono-substituted amino, di-substituted amino, halo(C₁₋₈ alkyl), haloalkyl and an optionally substituted C-carboxy.

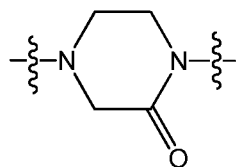
[0227] In some embodiments, a compound of Formula (II) with L^b being (III) can be selected from the following compounds: 3000 and 3001.

Formula (II_m)

[0228] In some embodiments, L^b can be Formula (II_m):



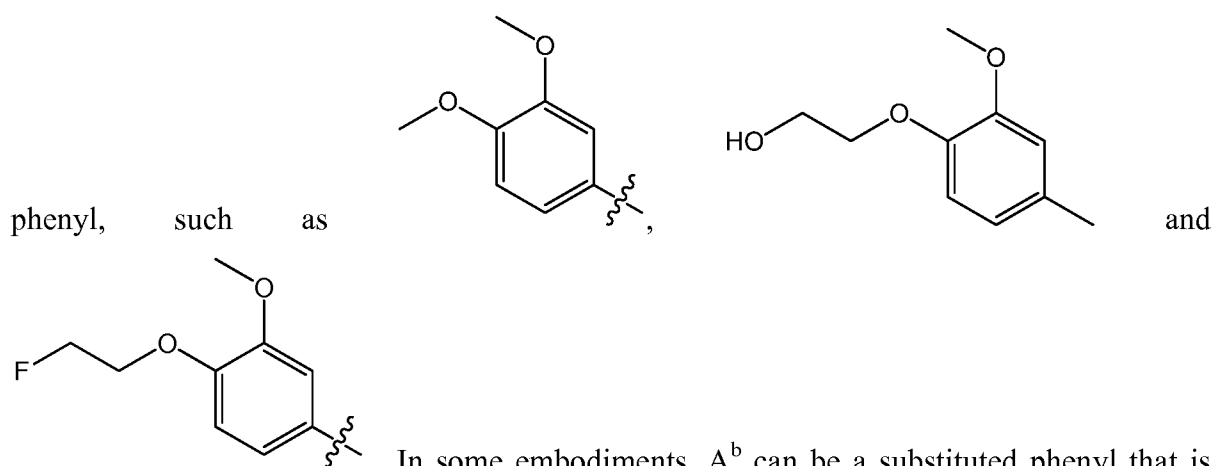
[0229] In some embodiments of Formula (II_m), ring B7 can be an optionally substituted heterocyclyl, such as an optionally substituted piperazinyl. In some embodiments, the optionally substituted piperazinyl can have the structure:



[0230] In some embodiments, a compound of Formula (II) with L^b being (II_m) can be compound 800.

[0231] In some embodiments, A^b can be substituted. In other embodiments, A^b can be unsubstituted.

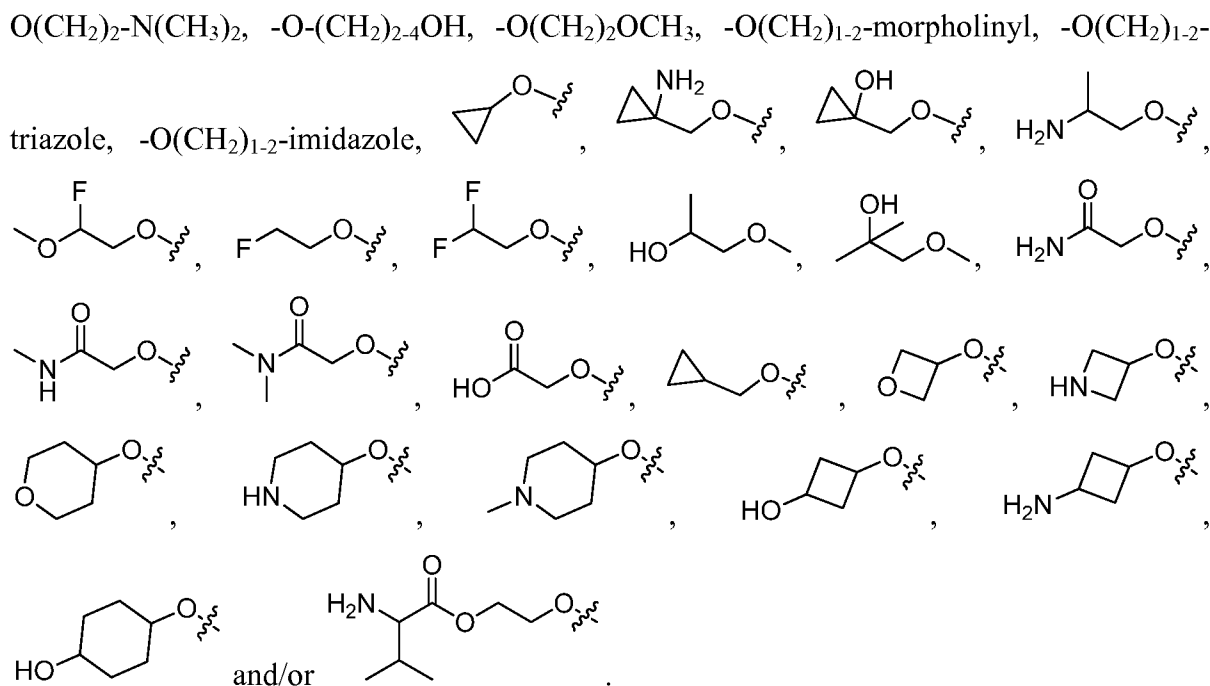
[0232] In some embodiments, A^b can be an optionally substituted aryl. For example, A^b can be an optionally substituted phenyl. In some embodiments, A^b can be a para-substituted phenyl, a meta-substituted phenyl or an ortho-substituted phenyl. In some embodiments, A^b can be a di-substituted phenyl. For example, A^b can be a 3,4-substituted



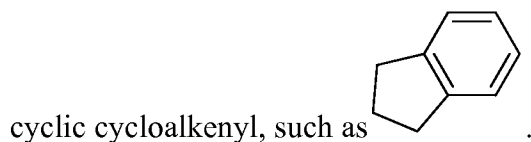
. In some embodiments, A^b can be a substituted phenyl that is substituted with 3 more substituents. In other embodiments, A^b can be unsubstituted phenyl. In some embodiments, A^b can be an optionally substituted naphthyl.

[0233] In some embodiments and without limitation, A^b 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 amine, sulfenyl, alkoxyalkyl, aryl, mono-cyclic heteroaryl, mono-cyclic 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, 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.

[0234] 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, N,N-di-methyl-amine, N,N-di-ethyl-amine, N-methyl-N-ethyl-amine, N-methyl-amino, N-ethyl-amino, amino, alkylthio (such as CH_3CH_2S-), phenyl, imidazole, morpholinyl, pyrazole, pyrrolidinyl, pyridinyl, piperidinyl, pyrrolidinone, pyrimidine, pyrazine, 1,2,4-oxadiazole, $-(CH_2)_{1-2}-NH(CH_3)$, $-O(CH_2)_2-NH_2$, $-O(CH_2)_2-NH(CH_3)$, -



[0235] In some embodiments, A^b 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^b can be an optionally substituted cycloalkenyl, for example, an optionally substituted cyclohexenyl. In some embodiments, A^b can be an optionally substituted bi-



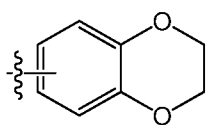
[0236] In some embodiments, A^b can be an optionally substituted aryl(C_{1-2} alkyl). In some embodiments, A^b can be an optionally substituted benzyl.

[0237] In some embodiments, A^b can be an optionally substituted mono-cyclic heteroaryl. In some embodiments, A^b can be an optionally substituted mono-cyclic 5-membered heteroaryl. In other embodiments, A^b can be an optionally substituted mono-cyclic 6-membered heteroaryl. In some embodiments, A^b can be an optionally substituted bi-cyclic heteroaryl.

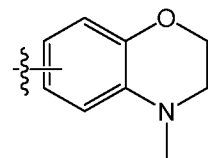
[0238] In some embodiments, the optionally substituted heteroaryl can be selected from an optionally substituted imidazole, an optionally substituted thiazole, an optionally substituted furan, an optionally substituted thiophene, an optionally substituted

pyrrole, an optionally substituted pyridine, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted quinolone, an optionally substituted imidazole, an optionally substituted oxazole and an optionally substituted isoxazole. In some embodiments, A^b can be an optionally substituted thiophene. In other embodiments, A^b can be an optionally substituted thiazole. In still other embodiments, A^b can be an optionally substituted pyridine. In yet still other embodiments, A^b can be an optionally substituted pyrimidine. In some embodiments, A^b can be an optionally substituted pyrazine. In other embodiments, A^b can be an optionally substituted imidazole.

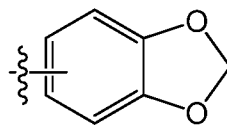
[0239] In some embodiments, A^b can be an optionally substituted heterocyclyl, for example, an optionally substituted mono-cyclic heterocyclyl or an optionally substituted bi-cyclic heterocyclyl. In some embodiments, A^b can be an optionally substituted



. In other embodiments, A^b can be an optionally substituted



In still other embodiments, A^b can be an optionally substituted



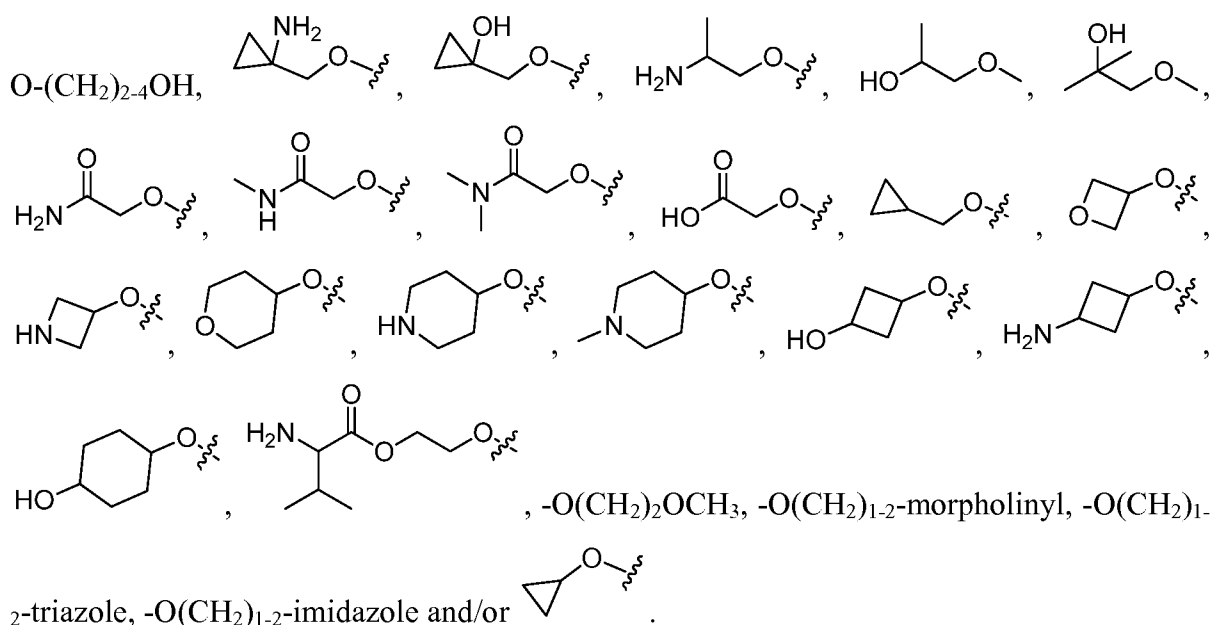
[0240] In some embodiments, A^b can be substituted with one or more R^C's. In some embodiments, one R^C can be present. In some embodiments, two R^C's can be present. In some embodiments, three R^C's can be present. In some embodiments, four or more R^C's can be present. When two or more R^C's are present, two or more R^C's can be the same or two or more R^C's can be different. In some embodiments, at least two R^C's can be the same. In some embodiments, at least two R^C's can be different. In some embodiments, all the R^C's can be the same. In other embodiments, all the R^C's can be different.

[0241] In some embodiments, R^C can be each independently selected from an unsubstituted C₁₋₄ alkyl, an optionally substituted C₁₋₄ alkyl, cycloalkyl, hydroxy, an optionally substituted C₁₋₄ alkoxy, C₁₋₄ alkoxy, halogen, haloalkyl, an optionally substituted haloalkoxy, nitro, amino, mono-substituted amino, di-substituted amine, sulfenyl, alkoxyalkyl, aryl, mono-cyclic heteroaryl, mono-cyclic heterocyclyl and aminoalkyl. In some embodiments, the optionally substituted C₁₋₄ alkoxy can be further substituted, for example, further substituted with a substituent selected from C₁₋₄ alkyl, halo, hydroxy, C-

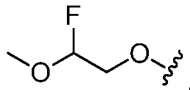
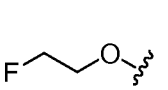
carboxy, C-amido, amino, mono-alkyl amine, di-alkyl amine and an amino acid. In some embodiments, the optionally substituted haloalkoxy can be further substituted, for example, further substituted with an C₁₋₄ alkoxy. In some embodiments, the optionally substituted heteroaryl can be further substituted, for example, further substituted with an C₁₋₄ alkyl.

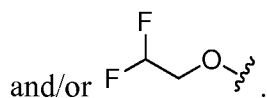
[0242] In some embodiments, each R^C can be an alkyl, such as methyl, ethyl, propyl (n-propyl and iso-propyl) and/or butyl (n-butyl, iso-butyl and t-butyl).

[0243] In some embodiments, each R^C 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(CH₂)₂-NH₂, -O(CH₂)₂-NH(CH₃), -O(CH₂)₂-N(CH₃)₂, -



[0244] In some embodiments, each R^C can be haloalkyl, for example, trifluoromethyl.

[0245] In some embodiments, each R^C can be an optionally substituted haloalkoxy, for example, difluoromethoxy, trifluoromethoxy, , ,



[0246] In some embodiments, each R^C can be halogen, for example, chloro, bromo and/or fluoro.

[0247] In some embodiments, each R^C can be amino, a mono-substituted amine or a di-substituted amine. For examples, R^C 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.

[0248] In some embodiments, each R^C can be hydroxy.

[0249] In some embodiments, each R^C can be alkylthio, for example ethylthio.

[0250] In some embodiments, each R^C can be aminoalkyl, such as $-(CH_2)_{1-2}-NH(CH_3)$.

[0251] In some embodiments, each R^C can be alkoxyalkyl, for example, $-CH_2-O-CH_3$.

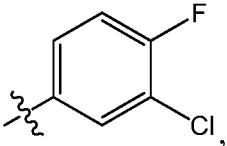
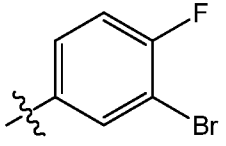
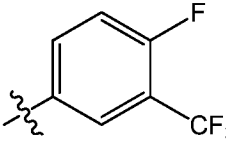
[0252] In some embodiments, each R^C can be aminoalkyl, for example, $-CH_2-NH_2$ or $-CH_2-N(CH_3)H$.

[0253] In some embodiments, each R^C can be an optionally substituted aryl, for example, an optionally substituted phenyl.

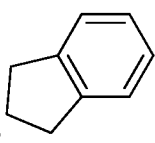
[0254] In some embodiments, each R^C can be an optionally substituted monocyclic heteroaryl, such as an optionally substituted imidazole, an optionally substituted pyrazole, an optionally substituted pyridinyl, an optionally substituted pyrimidine, an optionally substituted pyrazine and/or an optionally substituted 1,2,4-oxadiazole.

[0255] In some embodiments, each R^C 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.

[0256] In some embodiments, Y^b can be an optionally substituted aryl. In some embodiments, Y^b can be a para-substituted phenyl, a meta-substituted phenyl or an ortho-substituted phenyl. In some embodiments, Y^b can be a di-substituted phenyl, for example a di-halo substituted phenyl. For example, di-halo substituted phenyls include, but are not

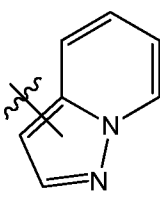
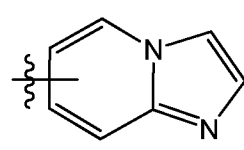
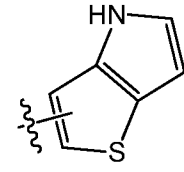
limited to, ,  and . In some embodiments, Y^b can be a substituted phenyl that is substituted with 3 more substituents. In other embodiments, Y^b can be unsubstituted phenyl. In some embodiments, Y^b can be a substituted naphthyl. In other embodiments, Y^b can be an unsubstituted naphthyl.

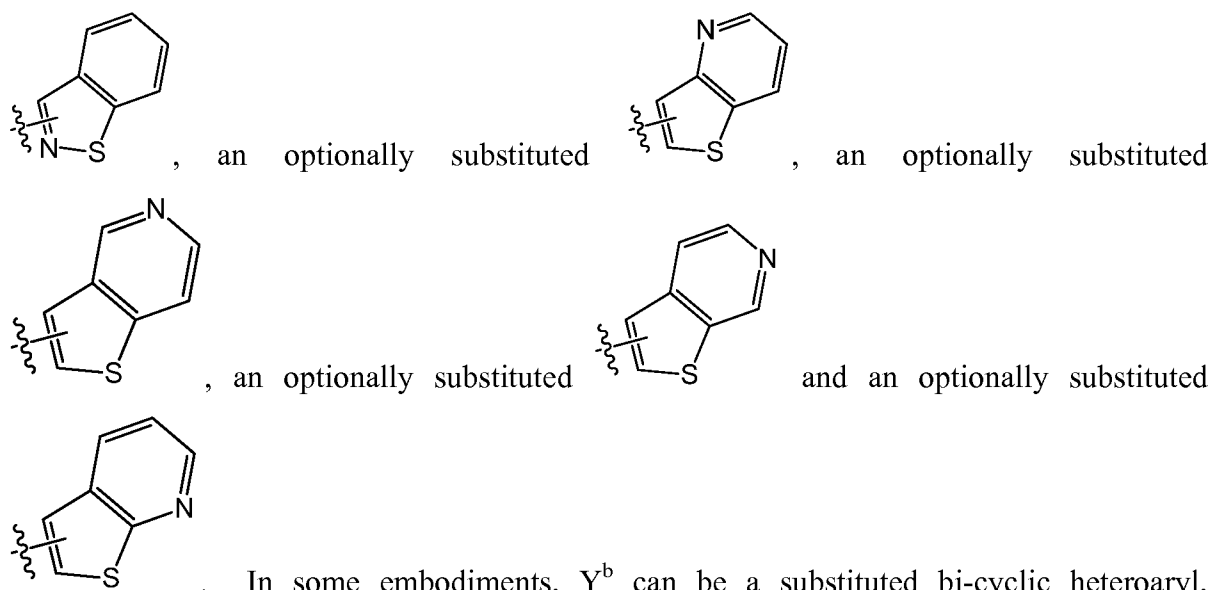
[0257] In some embodiments, Y^b can be an optionally substituted cycloalkyl (e.g., an optionally substituted cyclohexyl and an optionally substituted cycloheptyl). In some embodiments, Y^b can be an optionally substituted cycloalkenyl, for example, an optionally substituted cyclohexenyl. In some embodiments, Y^b can be an optionally

substituted bi-cyclic cycloalkenyl, such as .

[0258] In some embodiments, Y^b can be an optionally substituted mono-cyclic heteroaryl. In some embodiments, Y^b 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^b can be a substituted mono-cyclic heteroaryl, including those described herein. In some embodiments, Y^b can be an unsubstituted mono-cyclic heteroaryl, including those described herein.

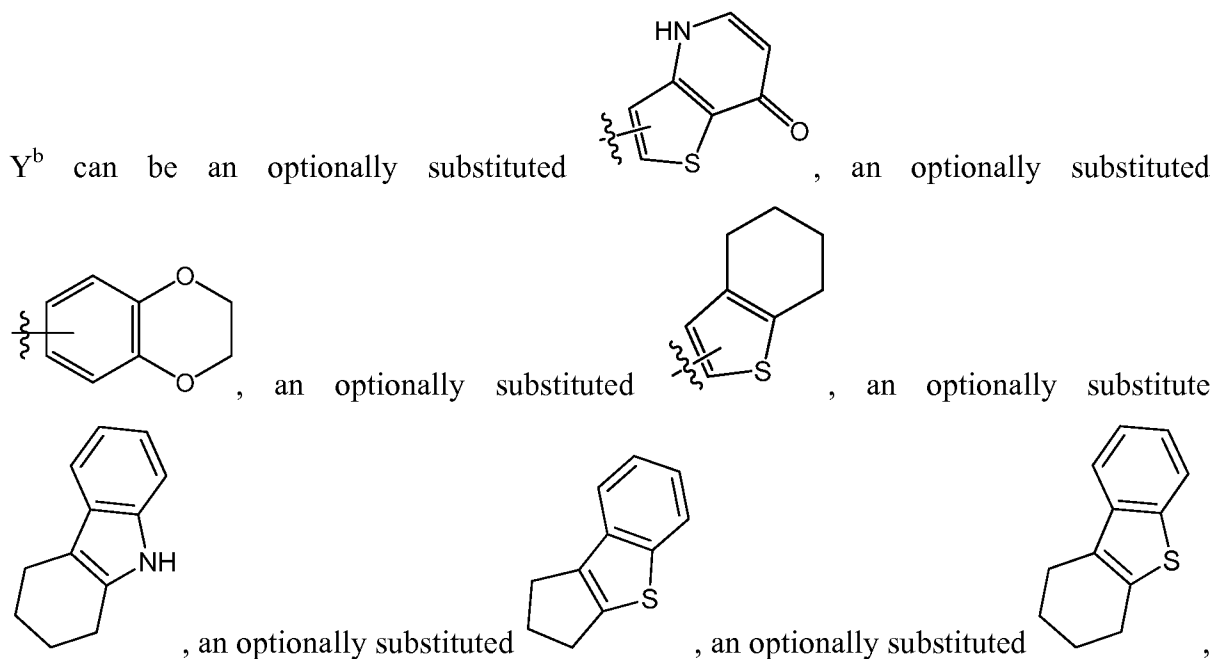
[0259] In some embodiments, Y^b can be an optionally substituted bi-cyclic heteroaryl. In some embodiments, Y^b can be selected from an optionally substituted benzothiophene, an optionally substituted benzofuran, an optionally substituted indole, an optionally substituted quinoline, an optionally substituted isoquinoline, an optionally substituted benzoxazole, an optionally substituted benzoisoxazole, an optionally substituted benzoisothiazole, an optionally substituted benzothiazole, an optionally substituted benzoimidazole, an optionally substituted benzotriazole, an optionally substituted 1H-indazole and an optionally substituted 2H-indazole. In some embodiments, Y^b can be

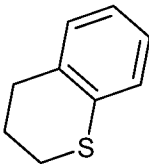
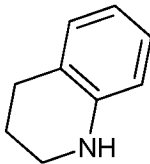
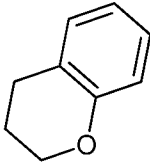
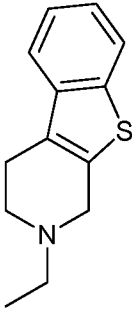
selected from an optionally substituted , an optionally substituted , an optionally substituted , an optionally substituted



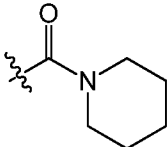
In some embodiments, Y^b can be a substituted bi-cyclic heteroaryl, including those described herein. In some embodiments, Y^b can be an unsubstituted bi-cyclic heteroaryl, including those described herein.

[0260] In some embodiments, Y^b can be an optionally substituted heterocyclyl. In some embodiments, Y^b can be an optionally substituted mono-cyclic heterocyclyl. In other embodiment, Y^b can be an optionally substituted bi-cyclic heterocyclyl. For example,

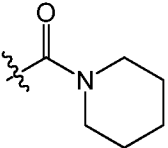


an optionally substituted , an optionally substituted , an optionally substituted  and/or an optionally substituted .

[0261] When Y^b is substituted, Y^b can be substituted with one or more R^D 's. In some embodiments, each R^D 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-

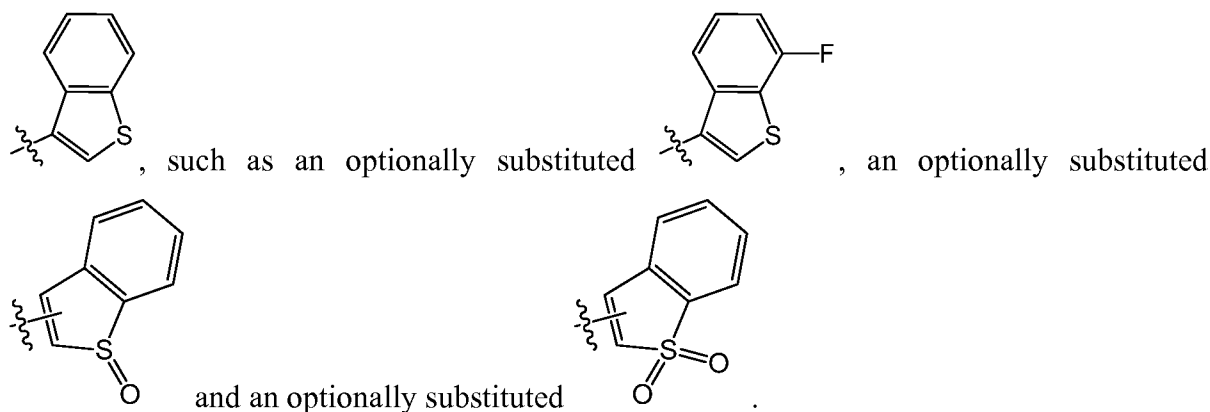
substituted amine and .

[0262] In some embodiments, when Y^b 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^b 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 C₁₋₄ alkyl, an optionally substituted phenyl and/or an unsubstituted acyl. In still other embodiments, when Y^b 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 C₁₋₄ alkyl, an optionally substituted phenyl, hydroxy, C₁₋₄ alkoxy, an unsubstituted acyl, carbonyl, cyano, amino, mono-C₁₋₄ alkyl amine and/or di-C₁₋₄ alkyl amine.

[0263] In some embodiments, Y^b can be an optionally substituted benzothiophene. In some embodiments, Y^b can be a substituted benzothiophene. In other embodiments, Y^b 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, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, NH₂ and/or mono-substituted amine. For example, the benzothiophene can be an optionally substituted



[0264] In some embodiments, Y^b can be an optionally substituted benzofuran.

[0265] In some embodiments, Y^b can be an optionally substituted indole. In some embodiments, Y^b can be a substituted indole. In some embodiments, the indole can be substituted 1, 2, 3 or more time with phenyl (substituted or unsubstituted), C₁₋₄ alkyl and/or halo. In other embodiments, Y^b can be an unsubstituted indole.

[0266] In some embodiments, Y^b can be substituted with one or more halogen. In some embodiments, Y^b can be substituted with one or more unsubstituted C₁₋₄ alkyl. In some embodiments, Y^b can be substituted with more or more hydroxy. In some embodiments, Y^b can be substituted with one or more optionally substituted phenyl. In some embodiments, Y^b can be substituted with one or more alkoxy. In some embodiments, Y^b can be substituted with one or more acyl. In some embodiments, Y^b can be substituted with one or more amino,

mono-substituted amino, or di-substituted amino. In some embodiments, Y^b can be substituted with one or more haloalkyl. In some embodiments, Y^b can be substituted with one or more haloalkoxy. In some embodiments, Y^b can be substituted with one or more C-carboxy. In some embodiments, Y^b can be substituted with one or more C-amido.

Pharmaceutical Compositions

[0267] 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0268] 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.

[0269] 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.

[0270] 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.

[0271] 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.

[0272] 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.

[0273] 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.

[0274] 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.

[0275] 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.

[0276] 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.

[0277] 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

[0278] 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing).

[0279] 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 a compound of Formula (I), or a pharmaceutically acceptable salt thereof, an effective amount of a compound of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing).

[0280] 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 a compound of Formula (I), or a pharmaceutically acceptable salt thereof, an effective amount of a compound of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing).

[0281] In some embodiments, the paramyxovirus infection is a human respiratory syncytial virus infection.

[0282] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the RSV polymerase complex.

[0283] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the hendravirus polymerase complex and/or nipahvirus polymerase complex.

[0284] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a

pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the measles polymerase complex.

[0285] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the mumps polymerase complex.

[0286] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the sendai virus polymerase complex.

[0287] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the

foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the HPIV-1 polymerase complex and/or HPIV-3 polymerase complex.

[0288] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the HPIV-2 polymerase complex and/or HPIV-4 polymerase complex.

[0289] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more

compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used to inhibit the human metapneumovirus polymerase complex.

[0290] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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).

[0291] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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).

[0292] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used treat and/or ameliorate croup due to a RSV infection and/or human parainfluenza virus 1 (HPIV-1) infection.

[0293] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, one or more compounds of Formula (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) can be used treat and/or ameliorate due to swelling of the salivary glands, fever, loss of appetite and/or fatigue due to mumps.

[0294] 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 (II), 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing) 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, and/or one or more compounds of Formula (II), 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, and/or one or more compounds of Formula (II), or a pharmaceutically acceptable salt thereof, can be used to treat HPIV-1 and/or HPIV-3.

[0295] The one or more compounds of Formula (I) or a pharmaceutically acceptable salt thereof, and/or one or more compounds of Formula (II), 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, and/or a compound of Formula (II), or a pharmaceutically acceptable salt thereof, provided in any of the embodiments described in paragraphs [0073]-[0266].

[0296] 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).

[0297] As used herein, the terms “treat,” “treating,” “treatment,” “therapeutic,” and “therapy” do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject’s overall feeling of well-being or appearance, and may positively affect one or more symptoms or aspects of the disease while having effects on other aspects of the disease or on unrelated systems that may be considered undesirable.

[0298] 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.

[0299] 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.

[0300] In some embodiments, an effective amount of a compound of Formulae (I) and/or(II), or a pharmaceutically acceptable salt of the foregoing, is an amount that is effective to reduce viral titers to essentially undetectable or very low levels, for example, to about 1000 to about 5000, to about 500 to about 1000, or to about 100 to about 500 genome copies/mL serum. In some embodiments, an effective amount of a compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, is an amount that is effective to reduce viral load compared to the viral load before administration of the compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing. For example, wherein the viral load is measured before administration of the compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, and again after completion of the treatment regime with the compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing (for example, 1 week after completion). In some embodiments, an effective amount of a compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, can be an amount that is effective to reduce viral load by 2x, 5x, 10x, 100x, 1000x, or more, or to lower than about 100 genome copies/mL serum. In some embodiments, an effective amount of a compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, is an amount that is

effective to 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 compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing. For example, wherein the viral load is measure before administration of the compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, and again after completion of the treatment regime with the compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing (for example, 1 week after completion).

[0301] In some embodiments, a compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, 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 after completion of the treatment regime (for example, 1 week after completion). In some embodiments, a compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, 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 Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, can result in a reduction of 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 paramyxovirus replication compared to the reduction of 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 week, two weeks, one month, two months, or three months, as compared to the reduction achieved after six months of ribavirin (Virazole®) therapy.

[0302] In some embodiments, an effective amount of a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, is an amount that is effective to achieve a sustained viral response, for example, non-detectable or substantially non-detectable paramyxovirus (e.g., less than about 500, less than about 400, less than about 200, or less than about 100 genome copies per milliliter serum) is found in the subject's serum for a period of at least about one week, two weeks, one month, at least

about two months, at least about three months, at least about four months, at least about five months, or at least about six months following cessation of therapy.

[0303] 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, compared to the development of RSV strains resistant to other RSV drugs.

[0304] In some embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, that experience complications can be 10% , 25%, 40%, 50%, 60%, 70%, 80% and 90% less compared to subjects being treated with ribavirin.

[0305] In some embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, 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 agents include but are not limited to ALN-

RSV01 (Alnylam Pharmaceuticals), ALN-RSV01 second generation (Alnylam Pharmaceuticals), CG-100 (Clarassance), STP-92 (Sirnaomics), iKT-041 (Inhibikase), BMS-433771 (1-cyclopropyl-3-[[1-(4-hydroxybutyl)benzimidazol-2-yl]methyl]imidazo[4,5-c]pyridin-2-one), RFI-641 ((4,4"-bis-{4,6-bis-[3-(bis-carbamoylmethyl-sulfamoyl)-phenylamino]-(1,3,5)triazin-2-ylamino}-biphenyl-2,2"-disulfonic-acid)), RSV604 ((S)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]di-azepin-3-yl)-urea), MDT-637 ((4Z)-2-methylsulfanyl-4-[(E)-3-thiophen-2-ylprop-2-enylidene]-1,3-thiazol-5-one), BTA9881, TMC-353121 (Tibotec), MBX-300, YM-53403 (N-cyclopropyl-6-[4-[(2-phenylbenzoyl)amino]benzoyl]-4,5-dihydrothieno[3,2-d][1]benzazepine-2-carboxamide), motavizumab (Medi-524, MedImmune), Medi-559, Medi-534 and Medi-557.

[0306] 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.

[0307] In some embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, can be administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, can be administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. For example, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, and at least one of the other additional agent(s) can be in a second pharmaceutical composition.

[0308] The order of administration of a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, with one or more additional agent(s) can vary. In some embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, can be administered prior to all additional agents. In other embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, can be administered prior to at least one additional agent. In still other embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, can be administered concomitantly with one or more additional agent(s). In yet still other embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, can be administered subsequent to the administration of at least one additional agent. In some embodiments, a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, can be administered subsequent to the administration of all additional agents.

[0309] A potential advantage of utilizing a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, in combination with one or more additional agent(s) described in paragraph [0305], including pharmaceutically acceptable salts and prodrugs thereof, may be a reduction in the required amount(s) of one or more compounds of paragraph [0305] (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 paragraph [0305], including pharmaceutically acceptable salts thereof, are administered without a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt the foregoing. For example, the amount of a compound described in paragraph [0305], including a pharmaceutically acceptable salt and prodrug thereof, can be less compared to the amount of the compound described in paragraph [0305], 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) and/or a compound of Formula (II), or a pharmaceutically acceptable salt of the foregoing, in

combination with one or more additional agent(s) described in paragraph [0305], 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.

[0310] Additional advantages of utilizing a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt the foregoing, in combination with one or more additional agent(s) described in paragraph [0305], including pharmaceutically acceptable salts and prodrugs thereof, may include little to no cross resistance between a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt the foregoing, and one or more additional agent(s) described in paragraph [0305] (including pharmaceutically acceptable salts and prodrugs thereof); different routes for elimination of a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt the foregoing, and one or more additional agent(s) described in paragraph [0305] (including pharmaceutically acceptable salts and prodrugs thereof); little to no overlapping toxicities between a compound of Formula (I) and/or a compound of Formula (II), or a pharmaceutically acceptable salt the foregoing, and one or more additional agent(s) described in paragraph [0305] (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 paragraph [0305], including pharmaceutically acceptable salts and prodrugs thereof).

[0311] 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.

[0312] 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.

[0313] In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compositions, a suitable human dosage can be inferred from ED₅₀ or ID₅₀ values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0314] 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.

[0315] 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.

[0316] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0317] 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

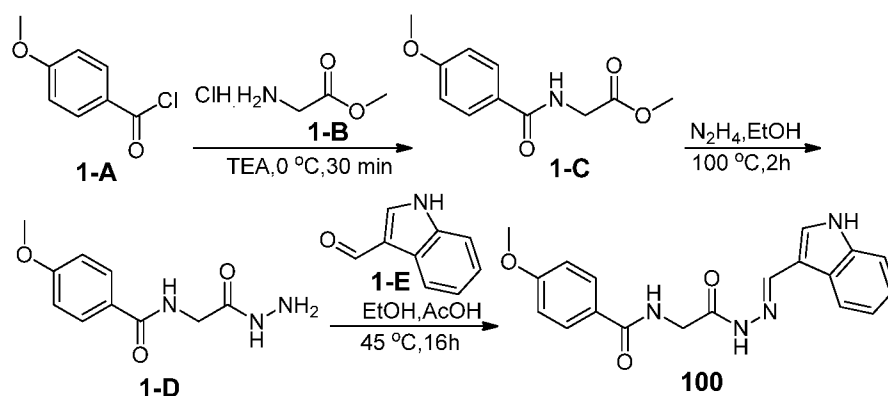
[0318] Compounds of Formulae (I) and Formula (II), and those described herein may be prepared in various ways. Some compounds of Formulae (I) and (II) can be obtained commercially and/or prepared utilizing known synthetic procedures. General synthetic routes to the compounds of Formulae (I) and (II), and some examples of starting materials used to synthesize the compounds of Formulae (I) and (II) 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

[0319] 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.

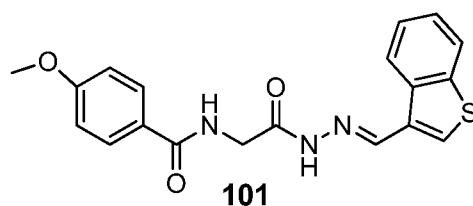
EXAMPLE 1 **Preparation of Compound 100**



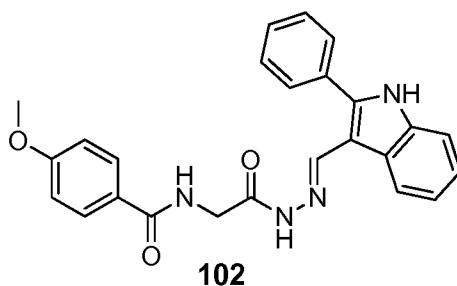
[0320] To a stirred solution of glycine methyl ester hydrochloride (**1-B**) (5.1 g, 40 mmol) in water and TEA (1:1, 40 mL) was added 4-methoxybenzoyl chloride (**1-A**) (4.0 g, 20 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 30 mins. The mixture was poured into saturated NaHCO₃ aq. cooled by ice bath, and then extracted with EA (ethyl acetate) and washed by brine, dried and concentrated to afford **1-C** (6.4 g, yield: 63%) as a white solid.

[0321] To a solution of **1-C** (6.40 g, 25.30 mmol) in anhydrous ethanol (50 mL) was added N₂H₄•H₂O (9.59 g, 191.80 mmol), the mixture was stirred at 100°C for 2 hours (h). Then the mixture was allowed to cool to room temperature (rt) and a white precipitate was formed in the solution. The precipitate was filtered and washed with EtOH (20 mL) to give **1-D** (5.8 g, 91.6%) as a white solid.

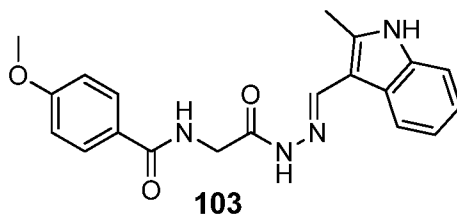
[0322] To a solution of **1-D** (115 mg, 0.5 mmol) in anhydrous ethanol (3 mL) was added **1-E** (80 mg, 0.5 mmol) and AcOH (0.1 mL), the mixture was stirred at 45°C for 16 h. Then the mixture was allowed to cool to rt and a white precipitate was formed in the solution. The precipitate was filtered and washed with EtOAc to afford compound **100** as a white solid (155 mg, 87.9%). +ESI-MS:m/z 351.0 [M+H]⁺.



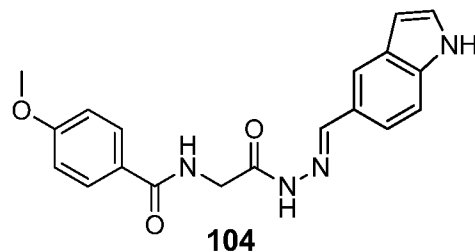
[0323] Compound **101** was obtained following the procedure for obtaining Compound **100** using the appropriate aldehyde in place of **1-E**. Compound **101** was obtained as a white solid (151 mg, 76.8%). +ESI-MS: m/z 368.0 $[M+H]^+$.



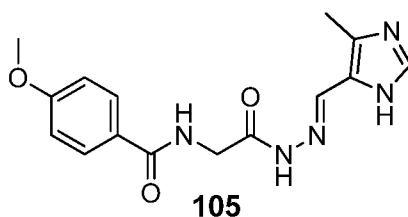
[0324] Compound **102** was obtained following the procedure for obtaining Compound **100** using the appropriate aldehyde in place of **1-E**. Compound **102** was obtained as a white solid (166 mg, 79.8%). +ESI-MS: m/z 427.0 $[M+H]^+$.



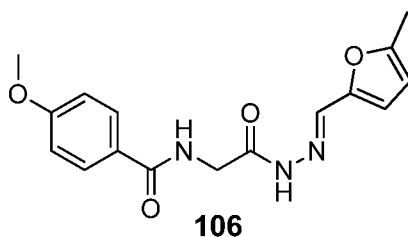
[0325] Compound **103** was obtained following the procedure for obtaining Compound **100** using the appropriate aldehyde in place of **1-E**. Compound **103** was obtained as a white solid (112 mg, 59.8%). +ESI-MS: m/z 365.0 $[M+H]^+$.



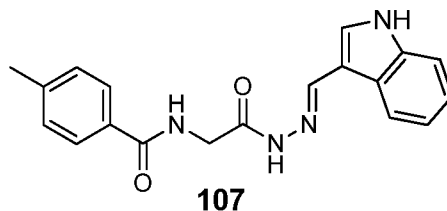
[0326] Compound **104** was obtained following the procedure for obtaining Compound **100** using the appropriate aldehyde in place of **1-E**. Compound **104** was obtained as a white solid (118 mg, 60.2%). +ESI-MS: m/z 351.0 $[M+H]^+$.



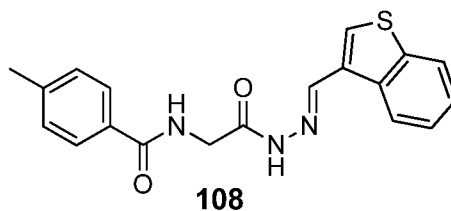
[0327] Compound **105** was obtained following the procedure for obtaining Compound **100** using the appropriate aldehyde in place of **1-E**. Compound **105** was obtained as a white solid (118 mg, 60.2%). +ESI-MS:m/z 316.0 [M+H]⁺.



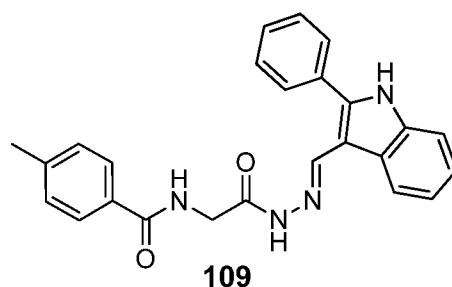
[0328] Compound **106** was obtained following the procedure for obtaining Compound **100** using the appropriate aldehyde in place of **1-E**. Compound **106** was obtained as a white solid (111 mg, 59.8%). +ESI-MS:m/z 316.0 [M+H]⁺.



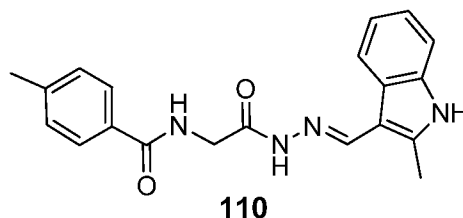
[0329] Compound **107** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A**. Compound **107** was obtained as a white solid (108 mg, 59.2%). +ESI-MS:m/z 335.0 [M+H]⁺.



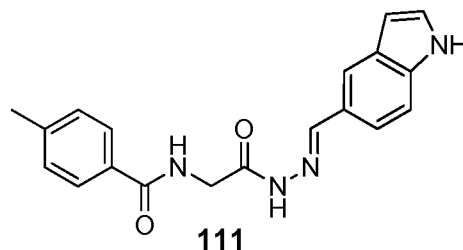
[0330] Compound **108** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **108** was obtained as a white solid (108 mg, 59.2%). +ESI-MS:m/z 352.0 [M+H]⁺.



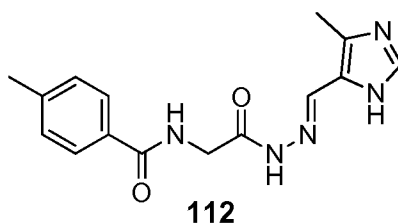
[0331] Compound **109** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **109** was obtained as a white solid (105 mg, 58.5%). +ESI-MS:m/z 411.0 [M+H]⁺.



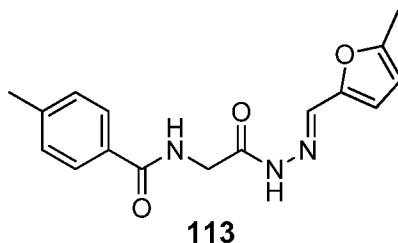
[0332] Compound **110** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **110** was obtained as a white solid (114 mg, 61.2%). +ESI-MS:m/z 349.0 [M+H]⁺.



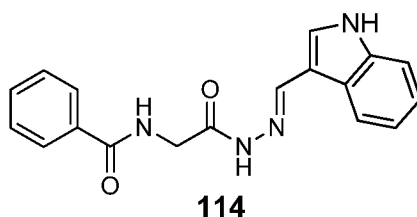
[0333] Compound **111** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **111** was obtained as a white solid (121 mg, 67.2%). +ESI-MS:m/z 335.0 [M+H]⁺.



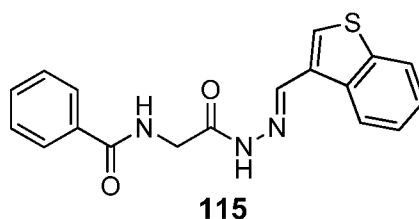
[0334] Compound **112** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **112** was obtained as a white solid (122 mg, 67.5%). +ESI-MS:m/z 300.0 [M+H]⁺.



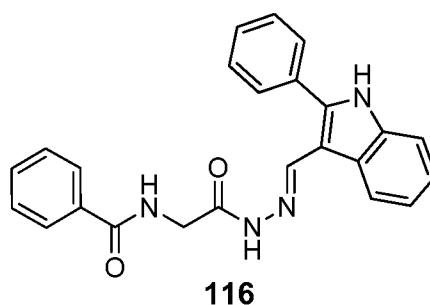
[0335] Compound **113** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **113** was obtained as a white solid (128 mg, 69.5%). +ESI-MS:m/z 300.0 [M+H]⁺.



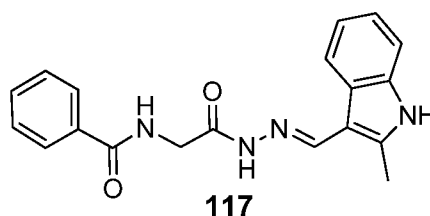
[0336] Compound **114** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A**. Compound **114** was obtained as a white solid (101 mg, 57.5%). +ESI-MS:m/z 321.0 [M+H]⁺.



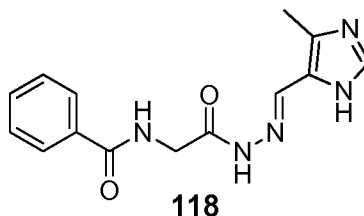
[0337] Compound **115** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **115** was obtained as a white solid (108 mg, 59.8%). +ESI-MS:m/z 338.0 [M+H]⁺.



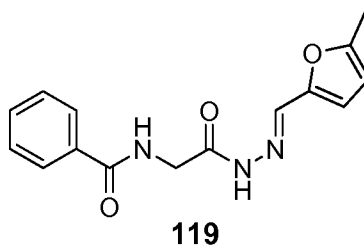
[0338] Compound **116** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **116** was obtained as a white solid (125 mg, 64.8%). +ESI-MS:m/z 397.0 [M+H]⁺.



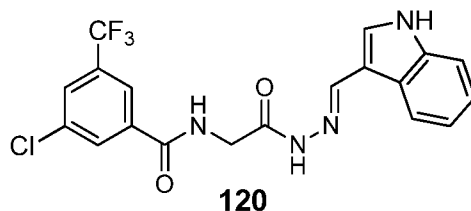
[0339] Compound **117** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **117** was obtained as a white solid (122 mg, 63.8%). +ESI-MS:m/z 335.0 [M+H]⁺.



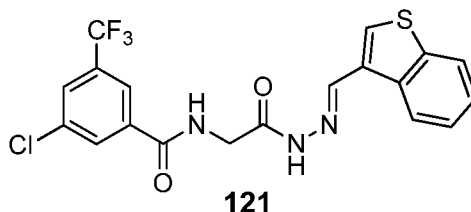
[0340] Compound **118** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **118** was obtained as a white solid (121 mg, 62.7%). +ESI-MS:m/z 286.0 [M+H]⁺.



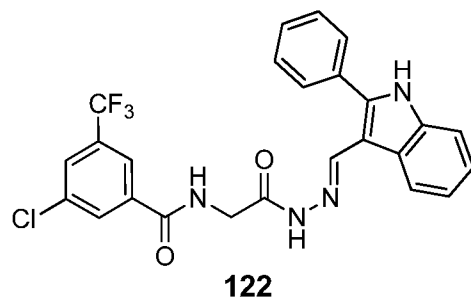
[0341] Compound **119** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **119** was obtained as a white solid (128 mg, 64.8%). +ESI-MS:m/z 286.0 [M+H]⁺.



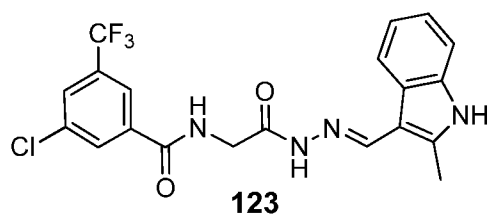
[0342] Compound **120** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A**. Compound **120** was obtained as a white solid (124 mg, 52.8%). +ESI-MS:m/z 423.0 [M+H]⁺.



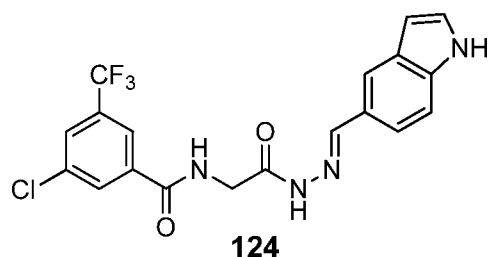
[0343] Compound **121** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **121** was obtained as a white solid (121 mg, 51.2%). +ESI-MS:m/z 440.0 [M+H]⁺.



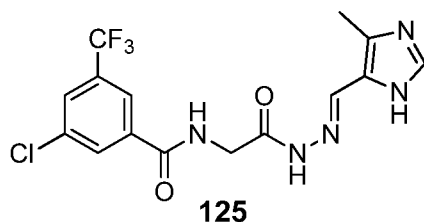
[0344] Compound **122** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **122** was obtained as a white solid (113 mg, 48.2%). +ESI-MS:m/z 499.0 [M+H]⁺.



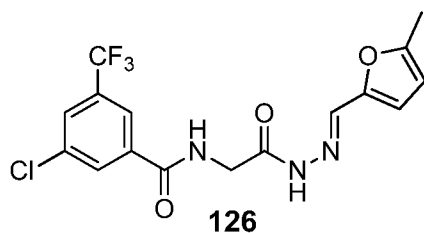
[0345] Compound **123** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **123** was obtained as a white solid (131 mg, 56.2%). +ESI-MS:m/z 437.0 [M+H]⁺.



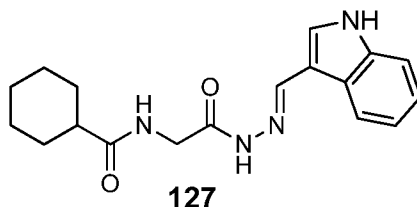
[0346] Compound **124** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **124** was obtained as a white solid (133 mg, 58.1%). +ESI-MS:m/z 423.0 [M+H]⁺.



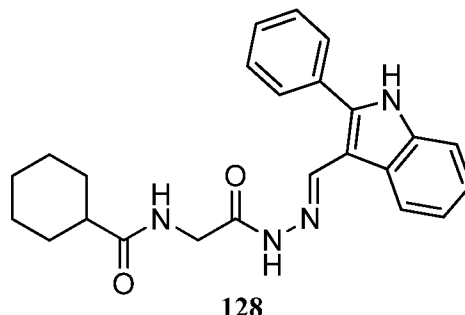
[0347] Compound **125** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **125** was obtained as a white solid (131 mg, 57.8%). +ESI-MS:m/z 388.0 [M+H]⁺.



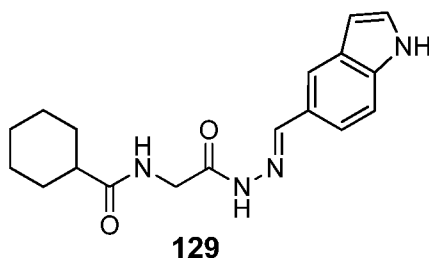
[0348] Compound **126** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **126** was obtained as a white solid (134 mg, 59.2%). +ESI-MS:m/z 388.0 [M+H]⁺.



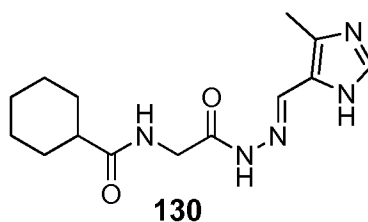
[0349] Compound **127** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A**. Compound **127** was obtained as a white solid (81 mg, 39.2%). +ESI-MS:m/z 327.0 [M+H]⁺.



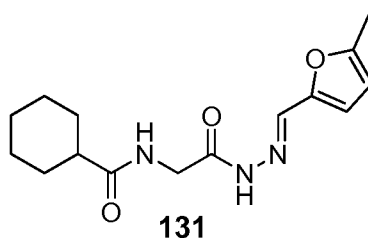
[0350] Compound **128** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **128** was obtained as a white solid (87 mg, 42.1%). +ESI-MS:m/z 403.0 [M+H]⁺.



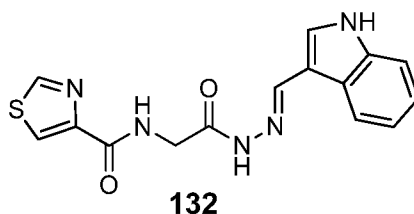
[0351] Compound **129** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **129** was obtained as a white solid (67 mg, 33.1%). +ESI-MS:m/z 327.0 [M+H]⁺.



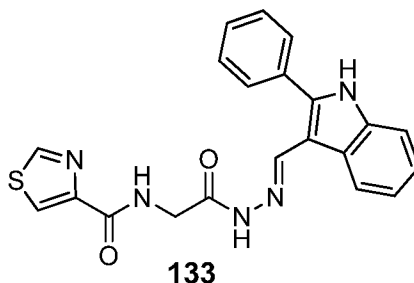
[0352] Compound **130** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **130** was obtained as a white solid (66 mg, 32.6%). +ESI-MS:m/z 292.0 [M+H]⁺.



[0353] Compound **131** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **131** was obtained as a white solid (58 mg, 30.6%). +ESI-MS:m/z 292.0 [M+H]⁺.

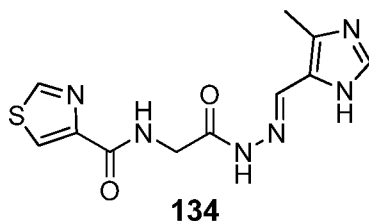


[0354] Compound **132** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A**. Compound **132** was obtained as a white solid (89 mg, 43.3%). +ESI-MS:m/z 328.0 [M+H]⁺.



[0355] Compound **133** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate

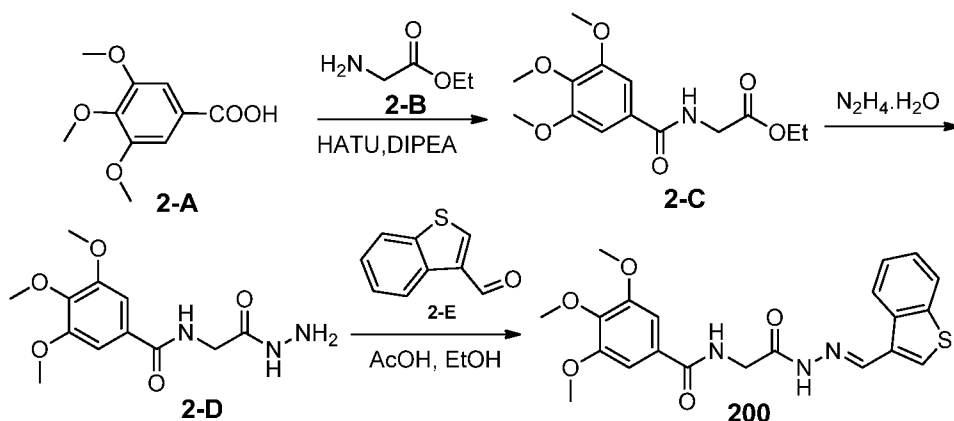
aldehyde in place of **1-E**. Compound **133** was obtained as a white solid (87 mg, 42.3%).
+ESI-MS:m/z 404.0 [M+H]⁺.



[0356] Compound **134** was obtained following the procedure for obtaining Compound **100** using the appropriate acid chloride in place of **1-A** and using the appropriate aldehyde in place of **1-E**. Compound **134** was obtained as a white solid (76 mg, 38.3%).
+ESI-MS:m/z 293.0 [M+H]⁺.

EXAMPLE 2

Preparation of Compound 200

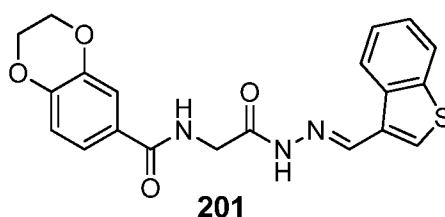


[0357] To a solution of 3,4,5-trimethoxybenzoic acid (**2-A**) (2.0 g, 9.43 mmol) in DCM (60 mL) was added HATU (5.4 g, 14.2 mmol) and DIPEA (5.0 g, 38.76 mmol), the mixture was stirred at room temperature for 30 mins, then was added glycine ethyl ester (**2-B**) (19.7 g, 14.2 mmol). The mixture was stirred at rt for another 15 h. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **2-C** as a white solid (1.5 g, 53.6%). +ESI-MS:m/z 297.9 [M+H]⁺.

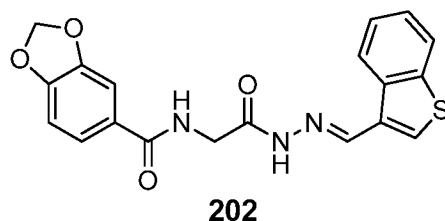
[0358] To a solution of **2-C** (1.54 g, 5.20 mmol) in anhydrous ethanol (50 mL) was added N₂H₄•H₂O (2.59 g, 80.9 mmol), the mixture was stirred at 80°C for 15 h. Then the mixture was allowed to cool to rt and a white precipitate was formed in the solution. The

precipitate was filtered and washed with EtOH (20 mL) to afford **2-D** as a white product (1.2 g, 81.6%). +ESI-MS:m/z 283.9 [M+H]⁺.

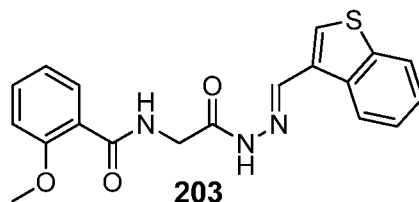
[0359] To a solution of **2-D** (200 mg, 0.71 mmol) in anhydrous ethanol (30 mL) was added benzo[*b*]thiophene-3-carbaldehyde (**2-E**) (150 mg, 0.92 mmol) and AcOH (0.1 mL), the mixture was stirred at 50°C for 15 h. Then the mixture was allowed to cool to rt and a white precipitate was formed in the solution. The precipitate was filtered and washed with EtOAc to afford compound **200** as a white solid (118 mg, 38.9%). +ESI-MS:m/z 428.0 [M+H]⁺.



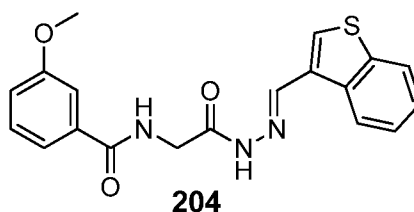
[0360] Compound **201** was obtained following the procedure for obtaining compound **200** using the 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **201** as obtained as a white solid (128 mg, 56.8%). +ESI-MS:m/z 396.0 [M+H]⁺.



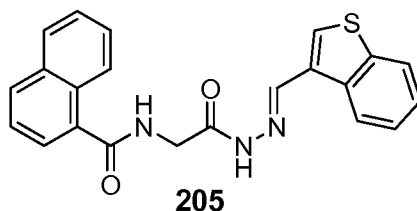
[0361] Compound **202** was obtained following the procedure for obtaining compound **200** using benzo[*d*][1,3]dioxole-5-carboxylic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **202** was obtained as a white solid (518 mg, 64.4%). +ESI-MS:m/z 381.9 [M+H]⁺.



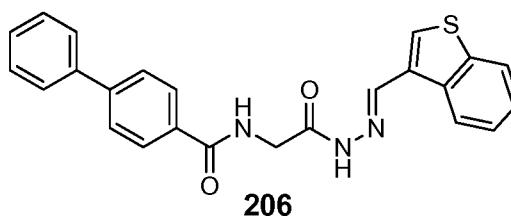
[0362] Compound **203** was obtained following the procedure for obtaining compound **200** using 2-methoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. +ESI-MS:m/z 368.0 [M+H]⁺.



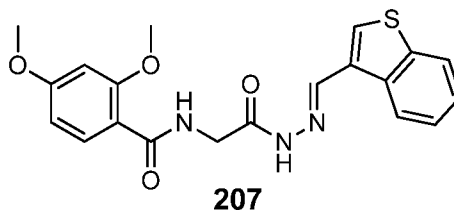
[0363] Compound **204** was obtained following the procedure for obtaining compound **200** using 3-methoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **204** was obtained as a white solid (179 mg, 68.2%). +ESI-MS:m/z 368.0 [M+H]⁺.



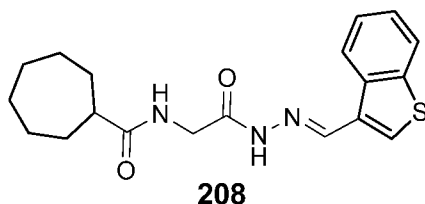
[0364] Compound **205** was obtained following the procedure for obtaining compound **200** using 1-naphthoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **205** was obtained as a white solid (672 mg, 81.3%). +ESI-MS:m/z 387.9 [M+H]⁺.



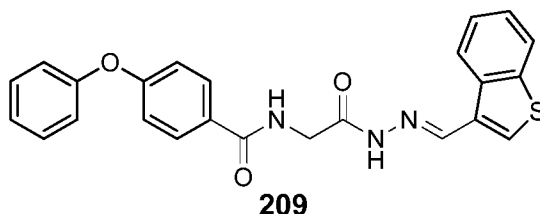
[0365] Compound **206** was obtained following the procedure for obtaining compound **200** using 4-phenyl benzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **206** was obtained as a white solid (167 mg, 90.8%). +ESI-MS:m/z 414.0 [M+H]⁺.



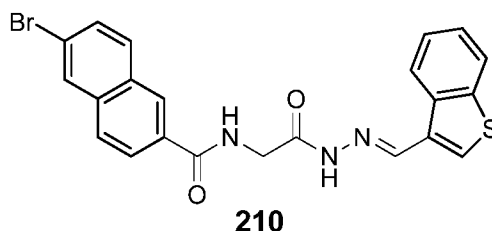
[0366] Compound **207** was obtained following the procedure for obtaining compound **200** using 2,4-dimethoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **206** was obtained as a white solid (130 mg, 57.8%). +ESI-MS:m/z 398.0 [M+H]⁺.



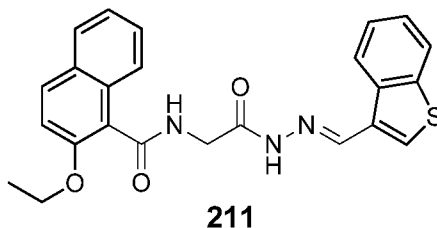
[0367] Compound **208** was obtained following the procedure for obtaining compound **200** using cycloheptanecarboxylic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **208** was obtained as a white solid (50 mg, 30.0%). +ESI-MS:m/z 358.0 [M+H]⁺



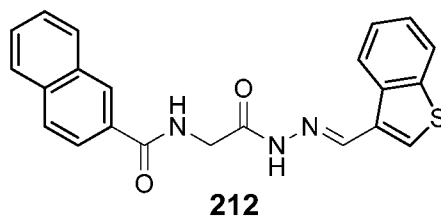
[0368] Compound **209** was obtained following the procedure for obtaining compound **200** using 4-phenoxybenzoic acid in place of **2-A**. Compound **209** was obtained as a white solid (60 mg, 40.0%). +ESI-MS:m/z 430.0 [M+H]⁺.



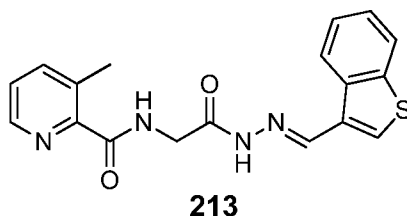
[0369] Compound **210** was obtained following the procedure for obtaining compound **200** using 6-bromo-2-naphthoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **210** was obtained as a white solid (50 mg, 35.0%). +ESI-MS:m/z 489.9 [M+Na]⁺



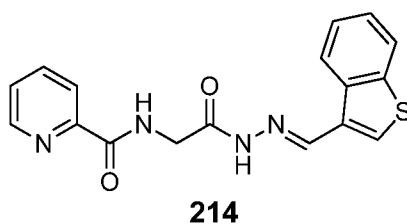
[0370] Compound **211** was obtained following the procedure for obtaining compound **200** using 2-ethoxy-1-naphthoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **211** was obtained as a white solid (60 mg, 40.0%). +ESI-MS:m/z 431.9 [M+H]⁺



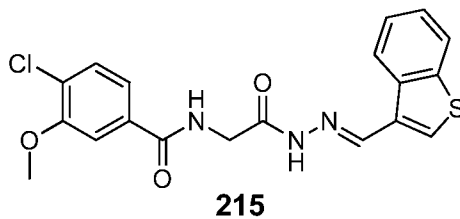
[0371] Compound **212** was obtained following the procedure for obtaining compound **200** using 2-naphthoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **212** was obtained as a white solid (70 mg, 43.7%). +ESI-MS:m/z 387.4 [M+H]⁺



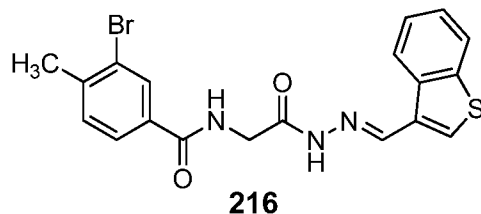
[0372] Compound **213** was obtained following the procedure for obtaining compound **200** using 3-methylpicolinic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **213** was obtained as a white solid (130.4 mg, 88.5%). +ESI-MS:m/z 352.9 [M+H]⁺.



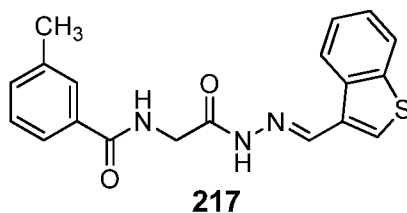
[0373] Compound **214** was obtained following the procedure for obtaining compound **200** using picolinic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **214** was obtained as a white solid (204.1 mg, 91.5%). +ESI-MS:m/z 338.9 [M+H]⁺.



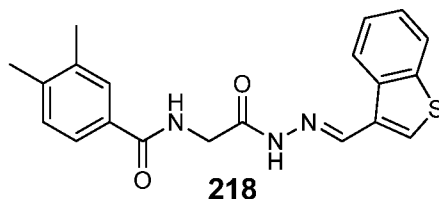
[0374] Compound **215** was obtained following the procedure for obtaining compound **200** using 4-chloro-3-methoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **215** was obtained as a white solid (46.3 mg, 65.8%). +ESI-MS:m/z 401.9 [M+H]⁺.



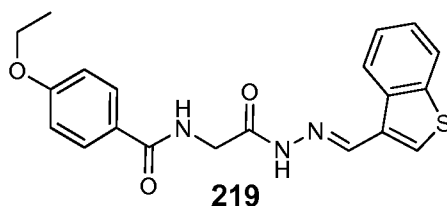
[0375] Compound **216** was obtained following the procedure for obtaining compound **200** using 3-bromo-4-methylbenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **216** was obtained as a white solid (68 mg, 22.7%). +ESI-MS:m/z 431.8 [M+H]⁺.



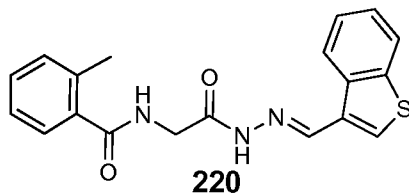
[0376] Compound **217** was obtained following the procedure for obtaining compound **200** using 3-methylbenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **217** was obtained as a white solid (92 mg, 36.5%). +ESI-MS:m/z 351.9 [M+H]⁺.



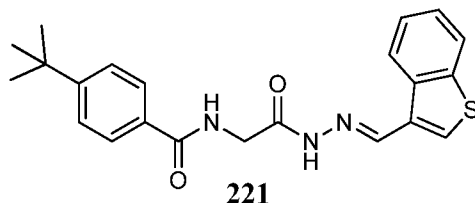
[0377] Compound **218** was obtained following the procedure for obtaining compound **200** using 3,4-dimethylbenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **218** was obtained as a white solid (40 mg, 42.4%). +ESI-MS:m/z 365.9 [M+H]⁺.



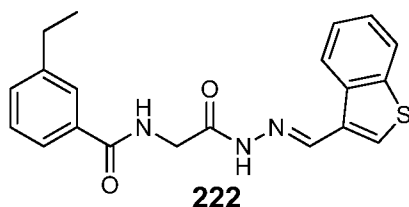
[0378] Compound **219** was obtained following the procedure for obtaining compound **200** using 4-ethoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **219** was obtained as a white solid (100 mg, 46.8%). +ESI-MS:m/z 381.9 [M+H]⁺.



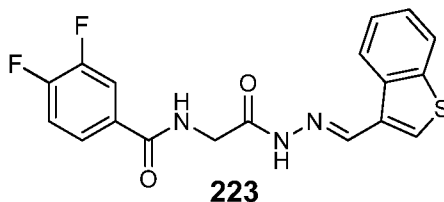
[0379] Compound **220** was obtained following the procedure for obtaining compound **200** using 2-methylbenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **220** was obtained as a white solid (40 mg, 23.7%). +ESI-MS:m/z 351.9 [M+H]⁺.



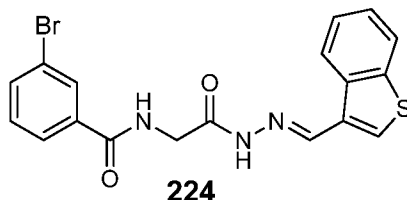
[0380] Compound **221** was obtained following the procedure for obtaining compound **200** using 4-(tert-butyl)benzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **221** was obtained as a white solid (57 mg, 53.2%). +ESI-MS:m/z 394.1 [M+H]⁺.



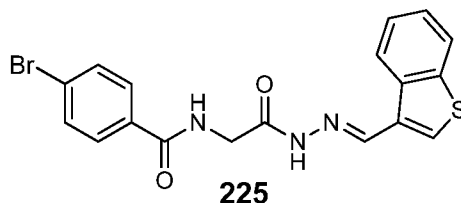
[0381] Compound **222** was obtained following the procedure for obtaining compound **200** using 4-(tert-butyl)benzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **222** was obtained as a white solid (75 mg, 22.8%). +ESI-MS:m/z 366.0 [M+H]⁺.



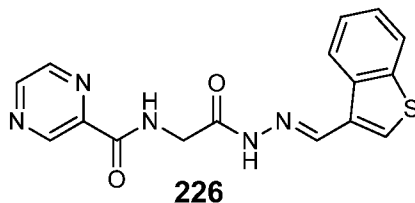
[0382] Compound **223** was obtained following the procedure for obtaining compound **200** using 3,4-difluorobenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **223** was obtained as a white solid (75 mg, 23.1%). +ESI-MS:m/z 373.9 [M+H]⁺.



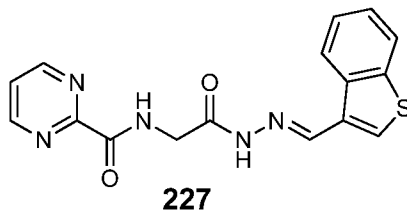
[0383] Compound **224** was obtained following the procedure for obtaining compound **200** using 3-bromobenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **224** was obtained as a white solid (124 mg, 40.3%). +ESI-MS:m/z 417.7 [M+H]⁺.



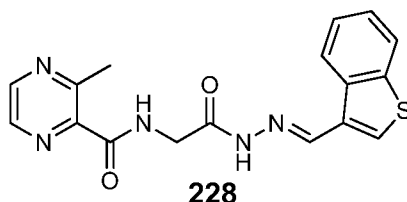
[0384] Compound **225** was obtained following the procedure for obtaining compound **200** using 4-bromobenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **225** was obtained as a white solid (160 mg, 51.9%). +ESI-MS:m/z 417.9 [M+H]⁺.



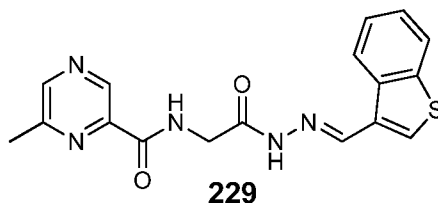
[0385] Compound **226** was obtained following the procedure for obtaining compound **200** using pyrazine-2-carboxylic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **226** was obtained as a white solid (3 mg, 7.8%). +ESI-MS:m/z 339.9 [M+H]⁺.



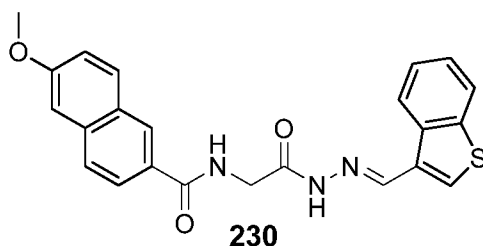
[0386] Compound **227** was obtained following the procedure for obtaining compound **200** using pyrimidine-2-carboxylic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **227** was obtained as a white solid (5 mg, 16.8%). +ESI-MS:m/z 339.9 [M+H]⁺.



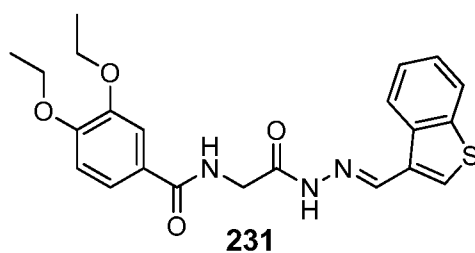
[0387] Compound **228** was obtained following the procedure for obtaining compound **200** using 3-methylpyrazine-2-carboxylic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **228** was obtained as a white solid (50 mg, 14.1%). +ESI-MS:m/z 353.9 [M+H]⁺.



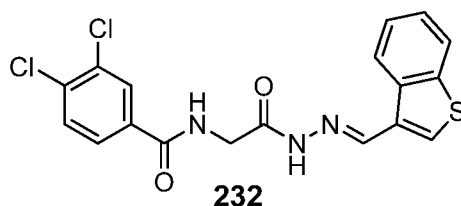
[0388] Compound **229** was obtained following the procedure for obtaining compound **200** using 4-methylpyrimidine-2-carboxylic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **229** was obtained as a white solid (10 mg, 11.3%). +ESI-MS:m/z 353.9 [M+H]⁺.



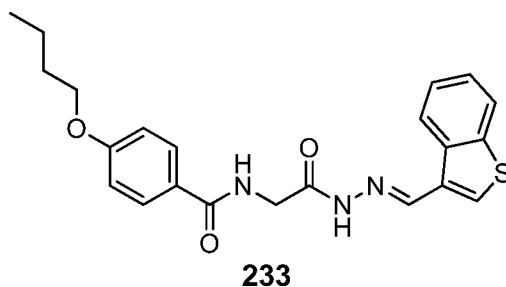
[0389] Compound **230** was obtained following the procedure for obtaining compound **200** using 6-methoxy-2-naphthoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **230** was obtained as a white solid (70 mg, 46.05%). +ESI-MS:m/z 418.1 [M+H]⁺.



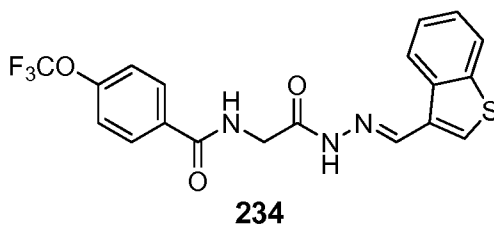
[0390] Compound **231** was obtained following the procedure for obtaining compound **200** using 3,4-diethoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **231** was obtained as a white solid (150 mg, 60%). ESI-LCMS: m/z 426 $[M+H]^+$.



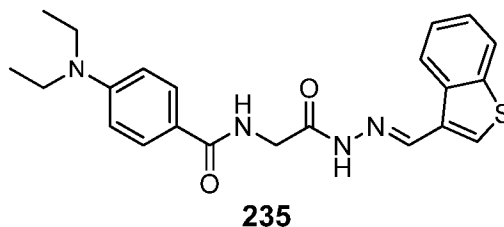
[0391] Compound **232** was obtained following the procedure for obtaining compound **200** using 3,4-dichlorobenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **232** was obtained as a white solid (154 mg, 62.5%). +ESI-MS: m/z 405.9 $[M+H]^+$.



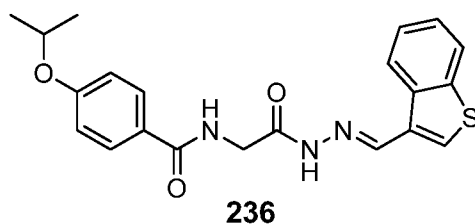
[0392] Compound **233** was obtained following the procedure for obtaining compound **200** using 4-butoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **233** was obtained as a white solid (60 mg, 20%). ESI-LCMS: m/z 409.9 $[M+H]^+$.



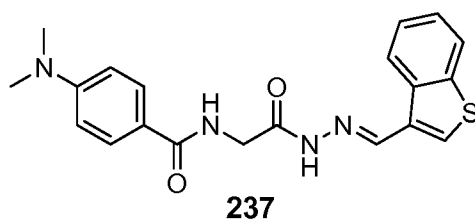
[0393] Compound **234** was obtained following the procedure for obtaining compound **200** using 4-(trifluoromethoxy)benzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **234** was obtained as a white solid (90 mg, 59.2%). +ESI-MS:m/z 443.8 [M+Na]⁺.



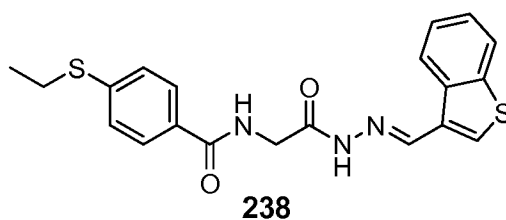
[0394] Compound **235** was obtained following the procedure for obtaining compound **200** using 4-(diethylamino)benzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **235** was obtained as a white solid (115 mg, 74.2%). +ESI-MS:m/z 409.1 [M+H]⁺.



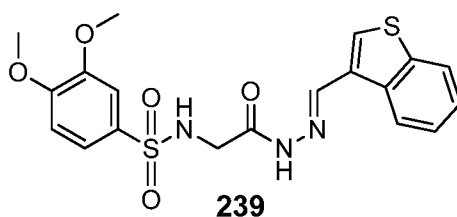
[0395] Compound **236** was obtained following the procedure for obtaining compound **200** using 4-isopropoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **236** was obtained as a white solid (15 mg, 25.8%). +ESI-MS:m/z 396.0 [M+H]⁺.



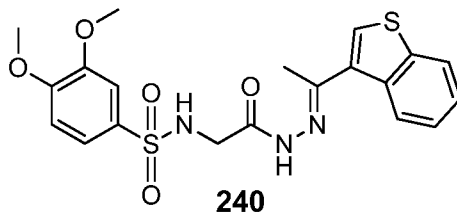
[0396] Compound **237** was obtained following the procedure for obtaining compound **200** using 4-(dimethylamino)benzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **237** was obtained as a white solid (80 mg, 20%). ESI-LCMS: m/z 381 [M+H]⁺.



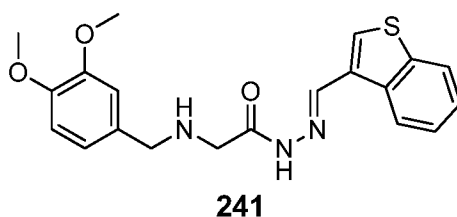
[0397] Compound **238** was obtained following the procedure for obtaining compound **200** using 4-(ethylthio)benzoic acid in place of 3,4,5-trimethoxybenzoic acid. Compound **238** was obtained as a white solid (80 mg, 34.1%). +ESI-MS: m/z 398.0 $[M+H]^+$.



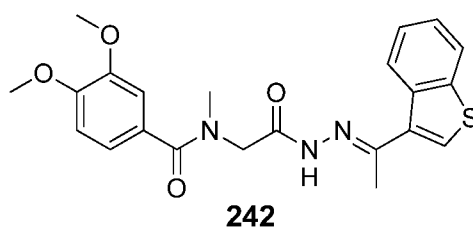
[0398] Compound **239** was obtained following the procedure for obtaining compound **200**. Compound **239** was obtained as a white solid (100 mg, 25.1%). ESI-LCMS: m/z 434.0 $[M+H]^+$.



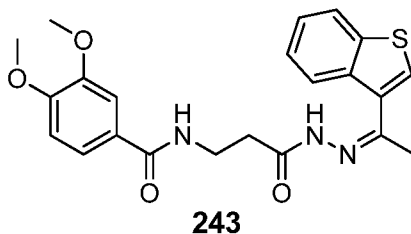
[0399] Compound **240** was obtained following the procedure for obtaining compound **239** using 1-(benzo[*b*]thiophen-3-yl)ethanone in place of benzo[*b*]thiophene-3-carbaldehyde. Compound **240** was obtained as a white solid (50 mg, 16.0%). ESI-LCMS: m/z 447.9 $[M+H]^+$.



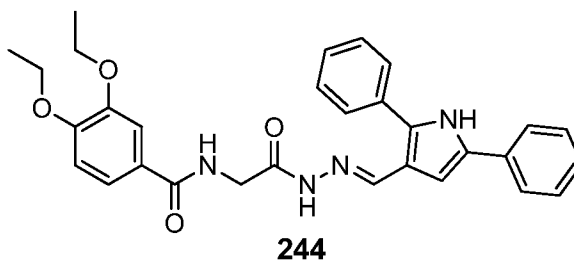
[0400] Compound **241** was obtained following the procedure for obtaining compound **200** using the appropriate acylhydrazine in place of **2-D**. Compound **241** was obtained as a white solid (22 mg, 18.3%). +ESI-MS: m/z 383.9 $[M+H]^+$.



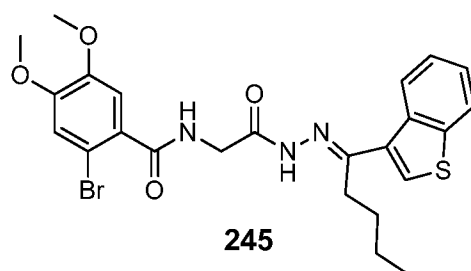
[0401] Compound **242** was obtained following the procedure for obtaining compound **200** using N-(2-hydrazinyl-2-oxoethyl)-3,4-dimethoxy-N-methylbenzamide in place of **2-D** and using 1-(benzo[b]thiophen-3-yl)ethanone in place of benzo[b]thiophene-3-carbaldehyde. Compound **242** was obtained as a white solid (8 mg, 11.2%). ESI-LCMS: m/z 426.2 $[M+H]^+$.



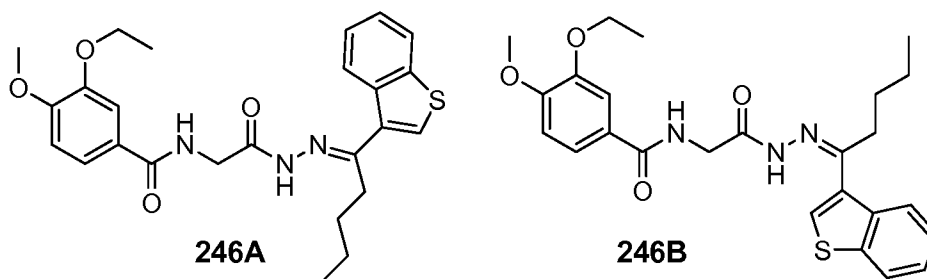
[0402] Compound **243** was obtained following the procedure for obtaining compound **200** using 3,4-dimethoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid and using 1-(benzo[b]thiophen-3-yl)ethanone in place of benzo[b]thiophene-3-carbaldehyde. Compound **243** was obtained as a white solid (120 mg, 52.2%). +ESI-MS: m/z 426.0 $[M+H]^+$.



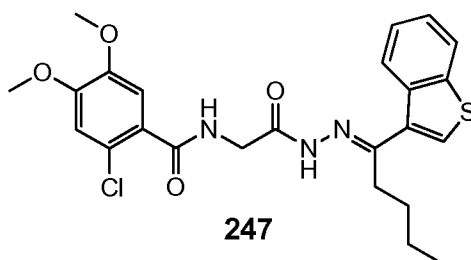
[0403] Compound **244** was obtained following the procedure for obtaining compound **200** using 3,4-diethoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid and using 2,5-diphenyl-1H-pyrrole-3-carboxaldehyde in place of benzo[b]thiophene-3-carbaldehyde. Compound **244** was obtained as a white solid (10 mg, 10.6%). ESI-LCMS: m/z 511.2 $[M+H]^+$.



[0404] Compound **245** was obtained following the procedure for obtaining compound **200** using 2-bromo-4,5-dimethoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid and using 1-(benzo[*b*]thiophen-3-yl)pentan-1-one in place of benzo[*b*]thiophene-3-carbaldehyde. Compound **245** was obtained as a white solid (128 mg, 56.8%). +ESI-MS:*m/z* 396.0 [M+H]⁺.



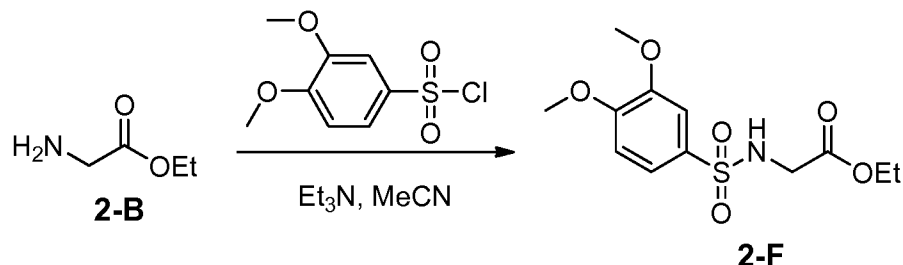
[0405] Compounds **246A** and **246B** were obtained following the procedure for obtaining compound **200** using 3-ethoxy-4-methoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid and using 1-(benzo[*b*]thiophen-3-yl)pentan-1-one in place of benzo[*b*]thiophene-3-carbaldehyde. Compound **246A** (25 mg, yield: 10.6%) and compound **246B** (5 mg, yield: 2.1%) were obtained as a white solid. Compound **246A**: +ESI-MS:*m/z* 467.89 [M+H]⁺. Compound **246B**: +ESI-MS:*m/z* 467.90 [M+H]⁺.



[0406] Compound **247** was obtained following the procedure for obtaining compound **200** using 2-chloro-4,5-dimethoxybenzoic acid in place of 3,4,5-trimethoxybenzoic acid and using 1-(benzo[*b*]thiophen-3-yl)pentan-1-one in place of

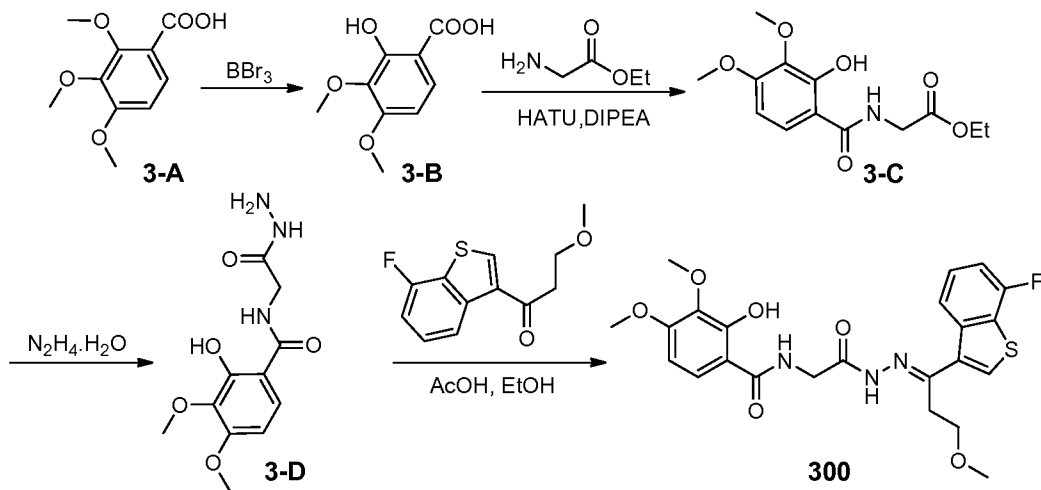
benzo[*b*]thiophene-3-carbaldehyde. Compound **247** was obtained as a white solid (85.2 mg, 33.5%). +ESI-MS:*m/z* 488.1 [M+H]⁺.

EXAMPLE 2-1
Preparation of Compound 2-F



[0407] To a solution of 3,4-dimethoxy-benzenesulfonyl chloride (1 g, 4.3 mmol) and glycine ethyl ester (**2-B**) (0.6 g, 4.3 mmol) in anhydrous MeCN (7.0 mL) was added triethylamine (2.0 mL) dropwise at 10°C. The solution was stirred at 50°C for 4 h and then cooled to rt. The precipitate was removed by filtration and the solid was washed with MeCN. The combined filtrate was concentrated in vacuo. The residue was crystallized from EtOH to afford **2-F** (0.8 g, 61%) used in next step directly without purification. +ESI-LCMS: *m/z* 303 [M+H]⁺.

EXAMPLE 3
Preparation of Compound 300



[0408] To a solution of 2,3,4-trimethoxybenzoic acid (**3-A**) (1.06 g, 5 mmol) in DCM (30 mL) was added BBr₃ (0.5 mL, 5.5 mmol) at -20°C, the mixture was stirred at -20°C for 30 mins. Then NaHCO₃ was added to quench the reaction. 2N HCl (50 mL) was

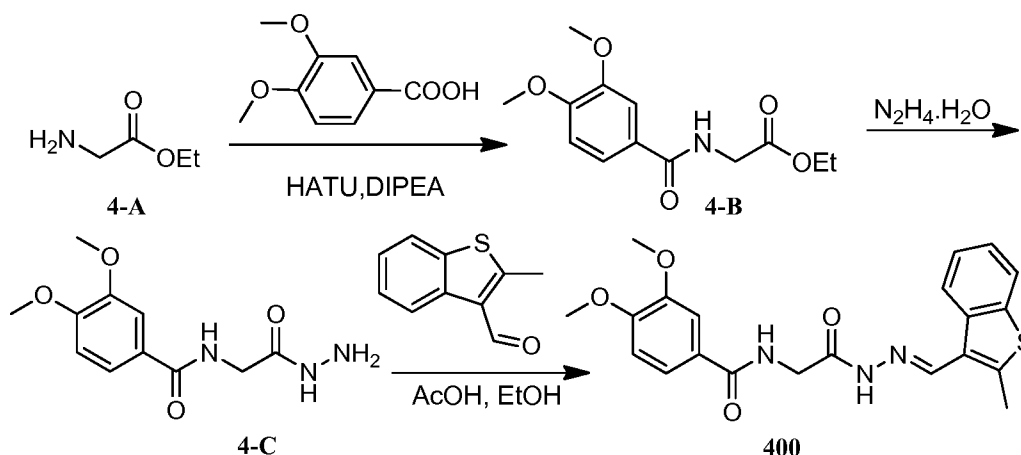
added and the mixture was extracted with DCM to afford 2-hydroxy-3,4-dimethoxybenzoic acid (**3-B**) (705 mg, 62.2%).

[0409] To a solution of 2-hydroxy-3,4-dimethoxybenzoic acid (**3-B**) (2.0 g, 9.43 mmol) in DCM (60 mL) was added HATU (5.4 g, 14.2 mmol) and DIPEA (5.0 g, 38.76 mmol), the mixture was stirred at rt for 30 mins, then was added glycine ethyl ester (19.7 g, 14.2 mmol). The mixture was stirred at rt for another 15 h. The mixture was washed with water and partitioned, the organic layer was collected. The solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **3-C** as a white solid (1.5 g, 53.6%).

[0410] To a solution of **3-C** (1.54 g, 5.20 mmol) in anhydrous ethanol (50 mL) was added $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (2.59 g, 80.9 mmol), the mixture was stirred at 80°C for 15 h. Then the mixture was allowed to cool to rt and the white precipitate was formed in the solution. The precipitate was filtered and washed with EtOH (20 mL) to afford **3-D** as a white product (1.2 g, 81.6%).

[0411] To a solution of **3-D** (93 mg, 0.31 mmol) in anhydrous ethanol (3 mL) was added 1-(7-fluorobenzo[*b*]thiophen-3-yl)-3-methoxypropan-1-one (50 mg, 0.21 mmol) and AcOH (0.1 mL), the mixture was stirred at 50°C for 15 h. Then the mixture was allowed to cool to rt and a white precipitate was formed. The precipitate was filtered and washed with EtOAc to afford compound **300** as a white solid (15 mg, 15.2%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.80 (m, 0.5H), 8.90-8.89 (m, 1H), 8.44-8.42 (m, 0.5H), 8.33 (s, 1H), 7.68-7.63 (m, 1H), 7.55-7.49 (m, 1H), 7.46-7.31 (m, 1H), 6.68-6.61 (m, 1H), 4.53-4.49 (m, 1H) 4.14 (d, $J = 5.2$ Hz, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.57-3.54 (m, 2H), 3.21-3.20 (m, 4H), 2.32-2.30 (m, 3H).

EXAMPLE 4
Preparation of Compound 400

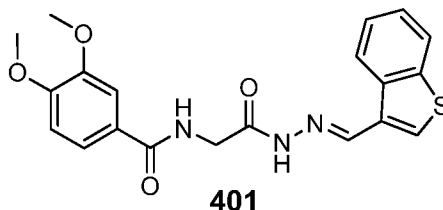


[0412] To a solution of 3,4-dimethoxy-benzoic acid (30 g, 0.19 mol) and HATU (80 g, 0.19 mol) in anhydrous DCM (600 mL) was added glycine ethyl ester (**4-A**) (26.7 g, 0.21 mol) and DIPEA (62 g, 0.48 mol) at 25°C. The solution was stirred for 10 h at this temperature and then diluted with 1.0 N aqueous NaHCO₃ solution (600 mL × 2), extracted with EA (500 mL × 2). The combined organic phase dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford **4-B** (40 g, 78.5%). ¹H NMR (DMSO, 400MHz) δ 8.81 (t, J = 6.0 Hz, 1H), 7.51-7.45 (dd, J₁ = 8.4 Hz, J₂ = 2.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.14-4.08 (m, 2H), 3.97 (d, J = 5.6 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H).

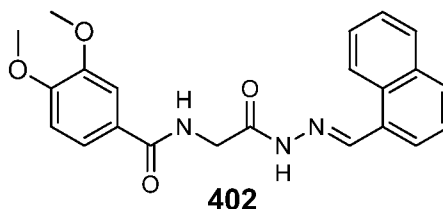
[0413] To a solution of **4-B** (40 g, 0.15 mol) in anhydrous EtOH (600 mL) was added NH₂NH₂·xH₂O (48 g, 1.5 mol). The solution was stirred for 10 h at 70°C and then cooled to rt. A precipitate was formed in the solution and was collected by filtration to afford **4-C** (37.5 g, 98.9%). ¹H NMR (DMSO-d₆, 400MHz) δ 9.11 (s, 1H), 8.59 (t, J = 6.0 Hz, 1H), 7.50-7.48 (dd, J₁ = 8.0 Hz, J₂ = 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.21 (s, 2H), 3.82 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H).

[0414] To a solution of **4-C** (200 mg, 0.79 mmol) in anhydrous EtOH (5 mL) and AcOH (0.3 mL) was added 2-methylbenzo[b]thiophene-3-carboxaldehyde (140 mg, 0.79 mmol). The solution was stirred at 70°C for 10 h and then cooled to rt. A precipitate was formed in the solution and was collected by filtration. The solid was washed with EA and

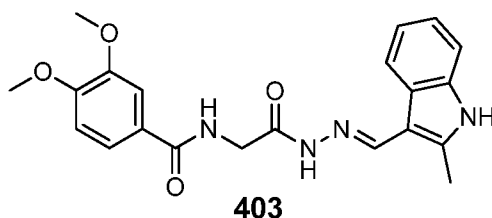
EtOH to give the compound **400** as a white solid (100 mg, 30%). ESI-LCMS:m/z 412 $[M+H]^+$.



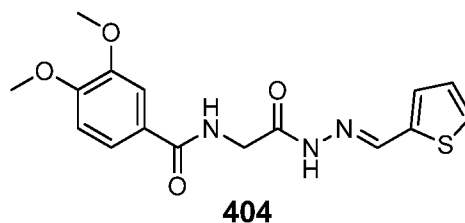
[0415] Compound **401** was obtained following the procedure for obtaining compound **400** using benzo[*b*]thiophene-3-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **401** was obtained as a white solid (177 mg, 56.4%). +ESI-MS:m/z 397.9 $[M+H]^+$.



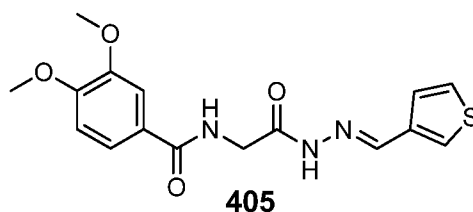
[0416] Compound **402** was obtained following the procedure for obtaining compound **400** using naphthalene-1-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **402** was obtained as a white solid (198.6 mg, 86.5%). ESI-MS:m/z 391.9 $[M+H]^+$.



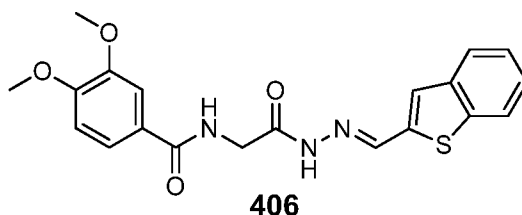
[0417] Compound **403** was obtained following the procedure for obtaining compound **400** using 2-methyl-1*H*-indole-3-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **403** was obtained as a white solid (50 mg, 30.2 %). ESI-MS:m/z 394 $[M+H]^+$.



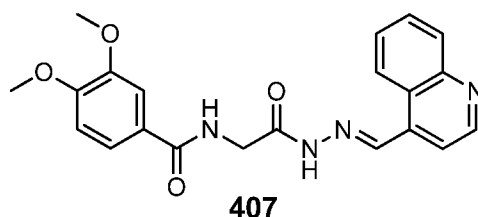
[0418] Compound **404** was obtained following the procedure for obtaining compound **400** using thiophene-2-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **404** was obtained as a white solid (60 mg, 20 %). ESI-MS:*m/z* 347.9 [M+H]⁺.



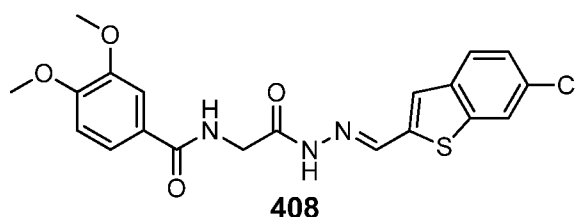
[0419] Compound **405** was obtained following the procedure for obtaining compound **400** using thiophene-3-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **405** was obtained as a white solid (100 mg, 40 %). ESI-MS:*m/z* 347.9 [M+H]⁺.



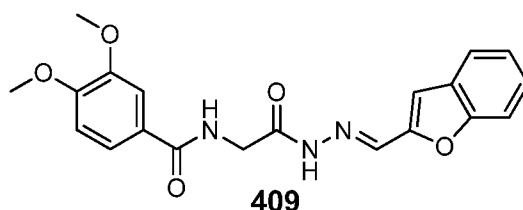
[0420] Compound **406** was obtained following the procedure for obtaining compound **400** using benzo[*b*]thiophene-2-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **406** was obtained as a white solid (120 mg, 42 %). ESI-MS:*m/z* 398 [M+H]⁺.



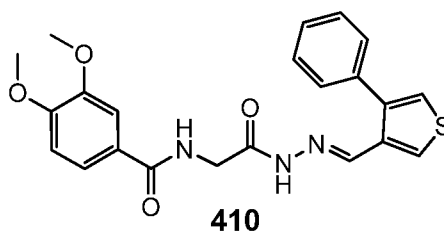
[0421] Compound **407** was obtained following the procedure for obtaining compound **400** using quinoline-4-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **407** was obtained as a white solid (70 mg, 50 %). ESI-LCMS: *m/z* 393 [M+H]⁺.



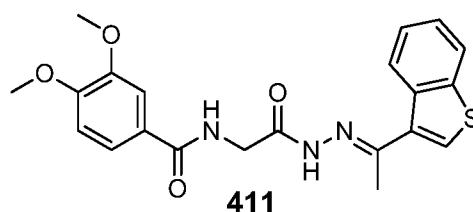
[0422] Compound **408** was obtained following the procedure for obtaining compound **400** using 6-chlorobenzo[*b*]thiophene-2-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **408** was obtained as a white solid (30 mg, 20 %). ESI-LCMS: m/z 432[M+H]⁺.



[0423] Compound **409** was obtained following the procedure for obtaining compound **400** using benzo[*b*]furan-2-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **409** was obtained as a white solid (50 mg, 20 %). ESI-LCMS: m/z 392 [M+H]⁺.

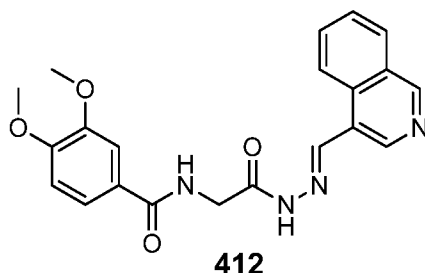


[0424] Compound **410** was obtained following the procedure for obtaining compound **400** using 3-phenyl-thiophene-2-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **410** was obtained as a white solid (63 mg, 55.7%). +ESI-MS: m/z 424.0 [M+H]⁺.

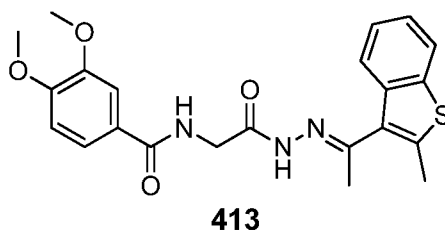


[0425] Compound **411** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-

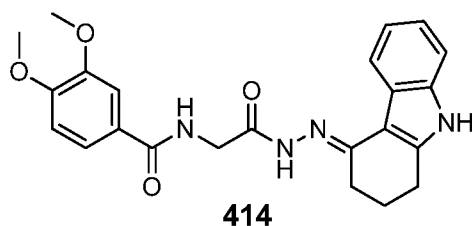
methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **411** was obtained as a white solid (80 mg, 25%). ESI-LCMS: m/z 412 $[M+H]^+$.



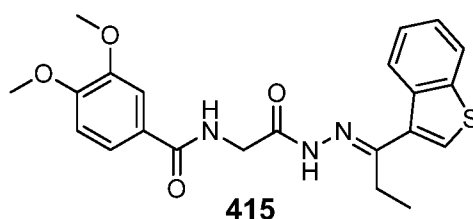
[0426] Compound **412** was obtained following the procedure for obtaining compound **400** using quinoline-4-carboxaldehyde in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **412** was obtained as a white solid (50 mg, 15%). ESI-LCMS: m/z 393 $[M+H]^+$.



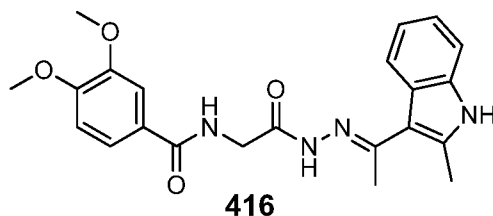
[0427] Compound **413** was obtained following the procedure for obtaining compound **400** using 1-(2-methylbenzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **413** was obtained as a white solid (180 mg, 55 %). +ESI-MS: m/z 425.9 $[M+H]^+$.



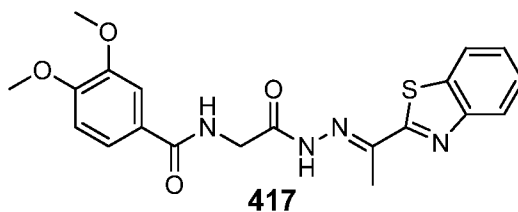
[0428] Compound **414** was obtained following the procedure for obtaining compound **400** using 2,3-dihydro-1*H*-carbazol-4(9*H*)-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **414** was obtained as a white solid (55 mg, 25 %). +ESI-MS: m/z 421.1 $[M+H]^+$.



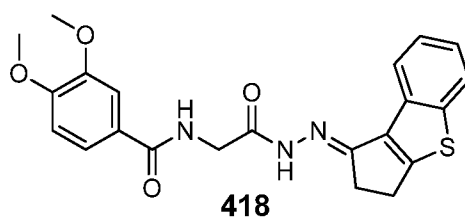
[0429] Compound **415** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)propan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **415** was obtained as a white solid (50 mg, 15%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.86-10.70 (br, 1H), 9.13-8.75 (m, 1H), 8.69-8.62 (m, 1H), 8.26 (d, $J_1 = 8.8$ Hz, 1H), 8.05-7.80 (m, 1H), 7.56-7.39 (m, 4H), 7.06 (d, $J_1 = 8.4$ Hz, 1H), 4.51 (d, $J = 5.6$ Hz, 1H), 4.15 (d, $J = 5.6$ Hz, 1H), 3.81 (s, 6 H), 2.91 (t, 2H), 1.16-1.09 (m, 3H). ESI-LCMS: m/z 426 [M+H]⁺.



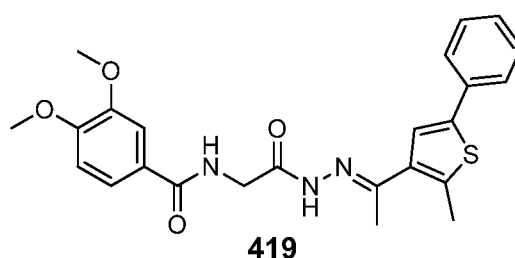
[0430] Compound **416** was obtained following the procedure for obtaining compound **400** using 1-(2-methyl-1*H*-indol-3-yl)propan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **416** was obtained as a white solid (20 mg, 12%). ESI-LCMS: m/z 409 [M+H]⁺.



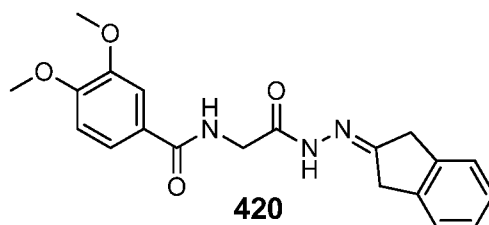
[0431] Compound **417** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*d*]thiazol-2-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **417** was obtained as a white solid (200 mg, 86 %). +ESI-MS: m/z 413.0 [M+H]⁺.



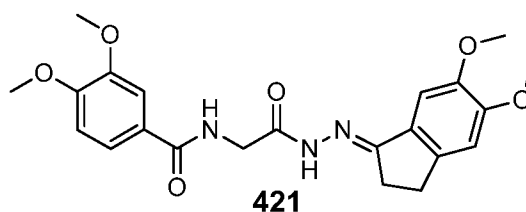
[0432] Compound **418** was obtained following the procedure for obtaining compound **400** using 2,3-dihydro-benzo[*b*]cyclopenta[*d*]thiophen-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **418** was obtained as a white solid (80 mg, 36 %). +ESI-MS:*m/z* 424.0 [M+H]⁺.



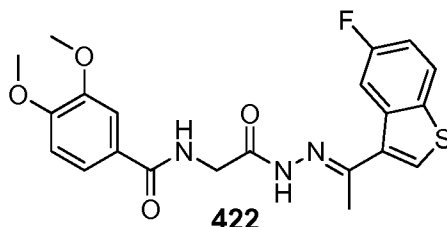
[0433] Compound **419** was obtained following the procedure for obtaining compound **400** using 1-(2-methyl-5-phenylthiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **419** was obtained as a white solid (60 mg, 20 %). ESI-LCMS:*m/z* 452 [M+H]⁺.



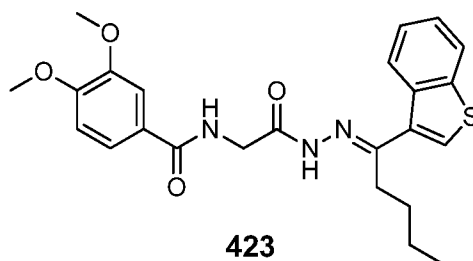
[0434] Compound **420** was obtained following the procedure for obtaining compound **400** using 1*H*-inden-2(3*H*)-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **420** was obtained as a white solid (101 mg, 55 %). +ESI-MS:*m/z* 368.0 [M+H]⁺.



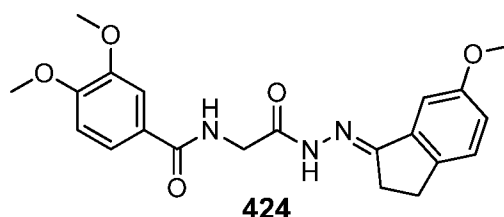
[0435] Compound **421** was obtained following the procedure for obtaining compound **400** using 2,3-dihydro-5,6-dimethoxyinden-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **421** was obtained as a white solid (98 mg, 45.8%). +ESI-MS: m/z 428.1 $[M+H]^+$.



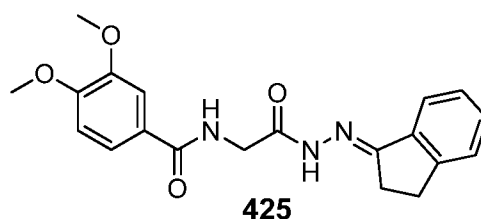
[0436] Compound **422** was obtained following the procedure for obtaining compound **400** using 1-(5-fluorobenzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **422** was obtained as a white solid (76 mg, 56.6%). +ESI-MS: m/z 429.8 $[M+H]^+$.



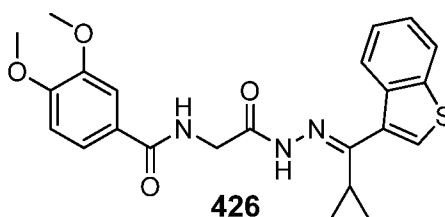
[0437] Compound **423** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)pentan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **423** was obtained as a white solid (700 mg, 67%). ESI-LCMS: m/z 454 $[M+H]^+$.



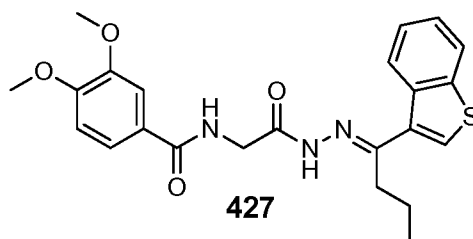
[0438] Compound **424** was obtained following the procedure for obtaining compound **400** using 2,3-dihydro-6-methoxyinden-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **424** was obtained as a white solid (80 mg, 15%). ESI-LCMS: m/z 398 $[M+H]^+$.



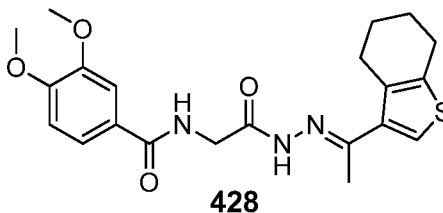
[0439] Compound **425** was obtained following the procedure for obtaining compound **400** using 2,3-dihydroinden-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **425** was obtained as a white solid (80 mg, 15%). ESI-LCMS: m/z 368 $[M+H]^+$.



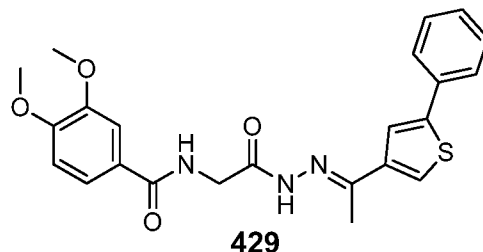
[0440] Compound **426** was obtained following the procedure for obtaining compound **400** using benzo[*b*]thiophen-3-yl(cyclopropyl)methanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **426** was obtained as a white solid (20 mg, 30.0%). +ESI-MS: m/z 438.1 $[M+H]^+$.



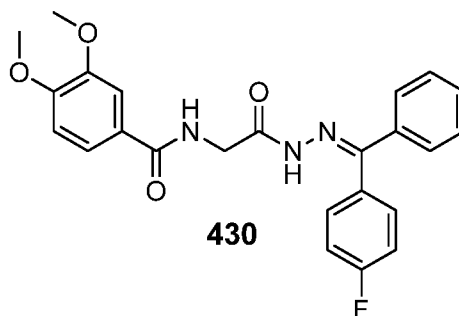
[0441] Compound **427** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)butan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **427** was obtained as a white solid (30 mg, 6 %). ESI-LCMS: m/z 440 $[M+H]^+$.



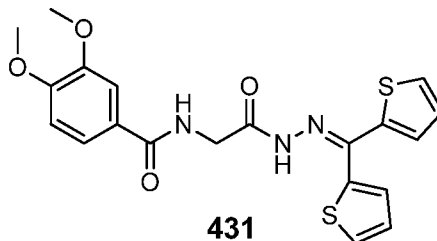
[0442] Compound **428** was obtained following the procedure for obtaining compound **400** using 1-(4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **428** was obtained as a white solid (7 mg, 38.42%). +ESI-MS: m/z 425.9 $[M+H]^+$.



[0443] Compound **429** was obtained following the procedure for obtaining compound **400** using 1-(5-phenylthiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **429** was obtained as a white solid (7 mg, 38.4%). +ESI-MS: m/z 438.1 $[M+H]^+$.

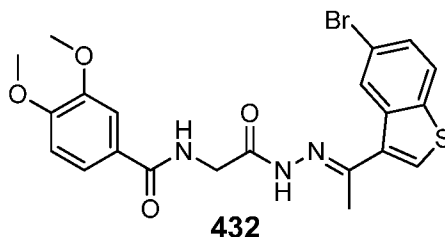


[0444] Compound **430** was obtained following the procedure for obtaining compound **400** using 4-fluorobenzophenone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **430** was obtained as a white solid (120 mg, 55 %). +ESI-MS: m/z 436.1 $[M+H]^+$.

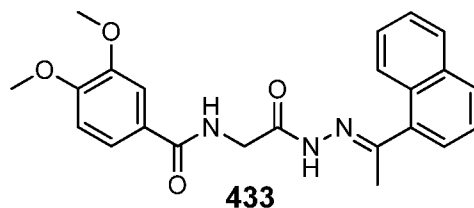


[0445] Compound **431** was obtained following the procedure for obtaining compound **400** using di-2-thienyl ketone in place of 2-methylbenzo[*b*]thiophene-3-

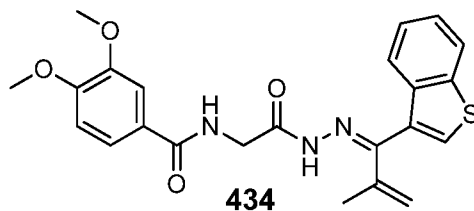
carboxaldehyde. Compound **431** was obtained as a white solid (76 mg, 75 %). +ESI-MS: m/z 430.0 $[M+H]^+$.



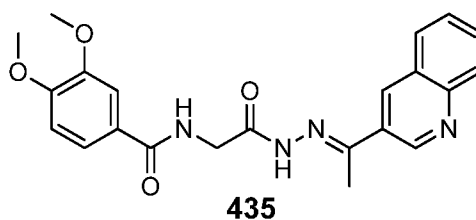
[0446] Compound **432** was obtained following the procedure for obtaining compound **400** using 1-(5-bromobenzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **432** was obtained as a white solid (80 mg, 37 %). +ESI-MS: m/z 491.6 $[M+H]^+$.



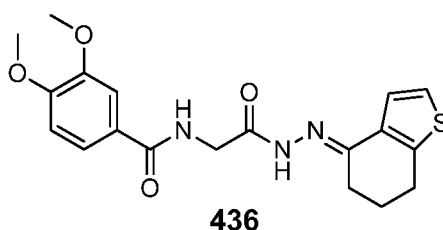
[0447] Compound **433** was obtained following the procedure for obtaining compound **400** using 1-(naphthalen-1-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **433** was obtained as a white solid (30 mg, 10 %). ESI-LCMS: m/z 406 $[M+H]^+$.



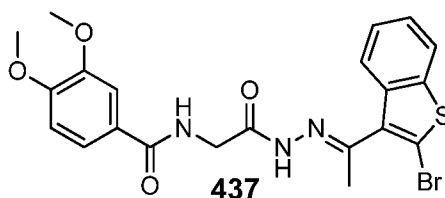
[0448] Compound **434** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)-2-methylprop-2-en-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **434** was obtained as a white solid (3 mg). ESI-LCMS: m/z 438 $[M+H]^+$.



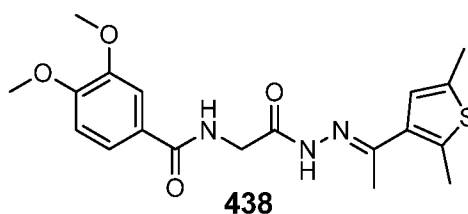
[0449] Compound **435** was obtained following the procedure for obtaining compound **400** using 1-(quinolin-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **435** was obtained as a white solid (85 mg, 50 %). +ESI-MS: m/z 407.0 $[M+H]^+$.



[0450] Compound **436** was obtained following the procedure for obtaining compound **400** using 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **436** was obtained as a white solid (146 mg, 57.48%). +ESI-MS: m/z 388.0 $[M+H]^+$.

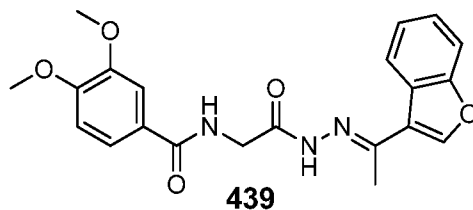


[0451] Compound **437** was obtained following the procedure for obtaining compound **400** using 1-(2-bromobenzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **437** was obtained as a white solid (50 mg, 12 %). +ESI-MS: m/z 490.1 $[M+H]^+$.

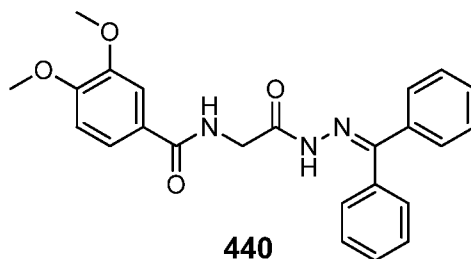


[0452] Compound **438** was obtained following the procedure for obtaining compound **400** using 1-(2,5-dimethylthiophen-3-yl)ethanone in place of 2-

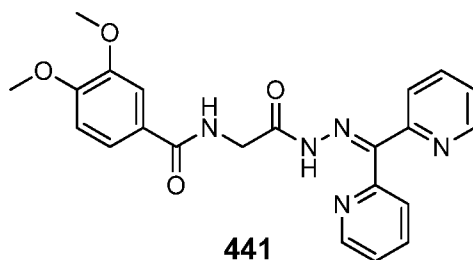
methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **438** was obtained as a white solid (50 mg, 13 %). ESI-LCMS: m/z 390 $[M+H]^+$.



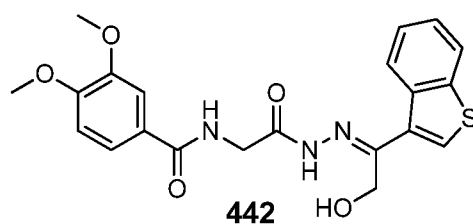
[0453] Compound **439** was obtained following the procedure for obtaining compound **400** using 1-(benzofuran-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **439** was obtained as a white solid (50 mg, 40 %). ESI-LCMS: m/z 396 $[M+H]^+$.



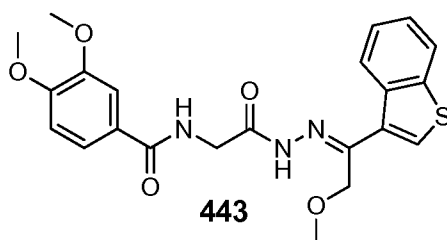
[0454] Compound **440** was obtained following the procedure for obtaining compound **400** using benzophenone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **440** was obtained as a white solid (10 mg). ESI-LCMS: m/z 418 $[M+H]^+$.



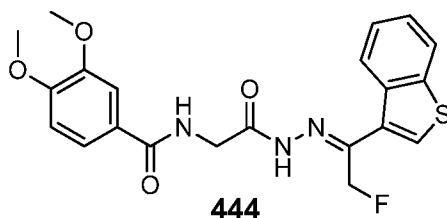
[0455] Compound **441** was obtained following the procedure for obtaining compound **400** using di(2-pyridyl) ketone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **441** was obtained as a white solid (100 mg, 20 %). ESI-LCMS: m/z 420 $[M+H]^+$.



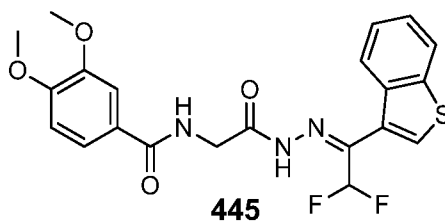
[0456] Compound **442** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)-2-hydroxyethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **442** was obtained as a white solid (62 mg, 14.5%). +ESI-MS: m/z 428.0 $[M+H]^+$.



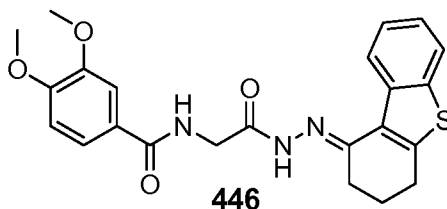
[0457] Compound **443** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)-2-methoxyethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **443** was obtained as a white solid (30 mg, 29.2%). +ESI-MS: m/z 442.0 $[M+H]^+$.



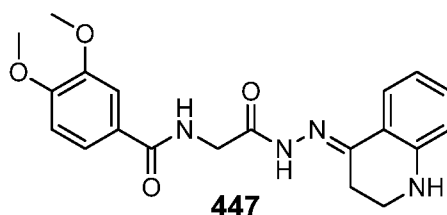
[0458] Compound **444** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)-2-fluoroethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **444** was obtained as a white solid (40 mg, 22.73%). +ESI-MS: m/z 430.8 $[M+H]^+$.



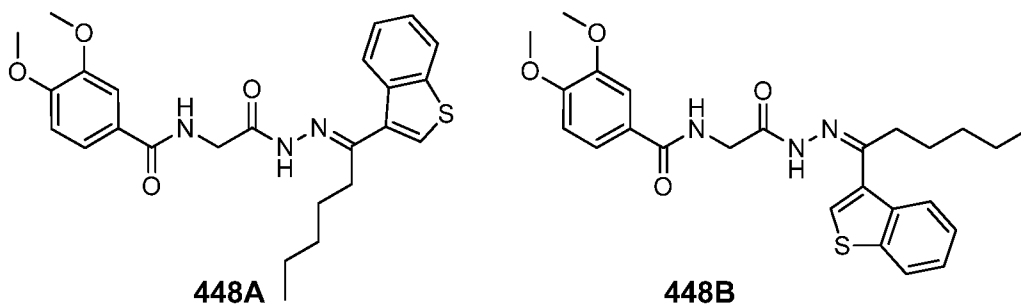
[0459] Compound **445** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)-2-difluoroethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **445** was obtained as a white solid (10 mg, 20.0 %). ESI-MS: m/z 448.0 $[M+H]^+$.



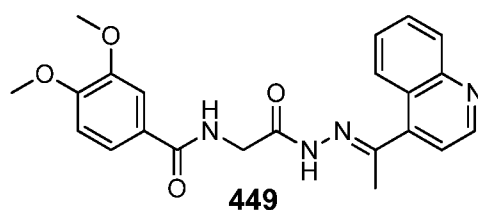
[0460] Compound **446** was obtained following the procedure for obtaining compound **400** using 3,4-dihydro-2H-dibenzothiophen-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **446** was obtained as a white solid (54 mg, 52 %). +ESI-MS: m/z 438.0 $[M+H]^+$.



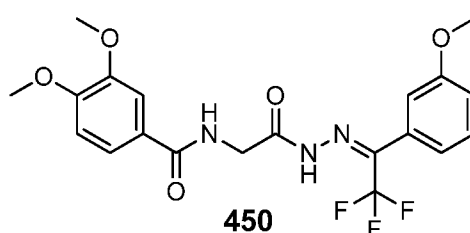
[0461] Compound **447** was obtained following the procedure for obtaining compound **400** using 2,3-dihydroquinolin-4(1H)-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **447** was obtained as a white solid (76 mg, 38 %). +ESI-MS: m/z 383.0 $[M+H]^+$.



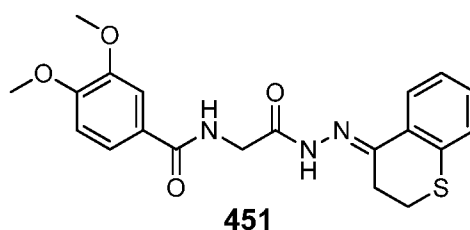
[0462] Compounds **448A** and **448B** were obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)hexan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compounds **448A** (70 mg, 10.0%) and **448B** (10 mg, 1.7%) were obtained as a white solid. Compound **448A**: +ESI-MS: m/z 467.9 $[M+H]^+$. Compound **448B**: +ESI-MS: m/z 467.9 $[M+H]^+$.



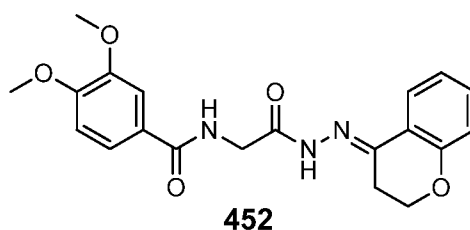
[0463] Compound **449** was obtained following the procedure for obtaining compound **400** using 4-acetylquinoline in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **449** was obtained as a white solid (50 mg, 30 %). ESI-LCMS: m/z 407 $[M+H]^+$.



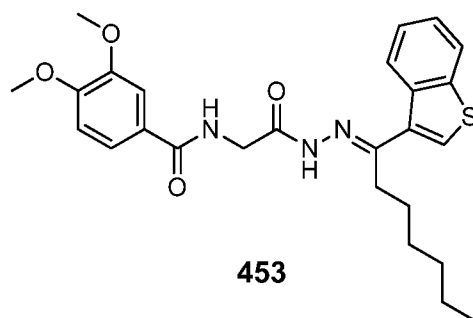
[0464] Compound **450** was obtained following the procedure for obtaining compound **400** using 3'-methoxy-2,2,2-trifluoroacetophenone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **450** was obtained as a white solid (8 mg). ESI-LCMS: m/z 440 $[M+H]^+$.



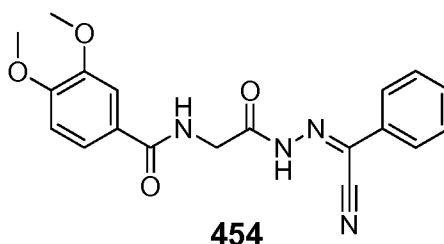
[0465] Compound **451** was obtained following the procedure for obtaining compound **400** using thiochroman-4-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **451** was obtained as a white solid (80 mg, 40 %). ESI-LCMS: m/z 400 $[M+H]^+$.



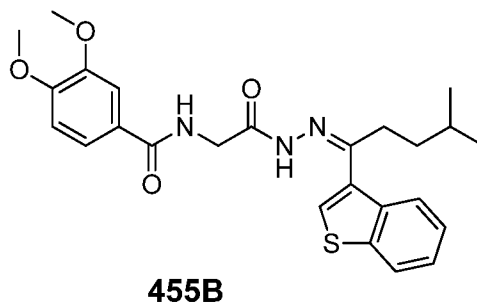
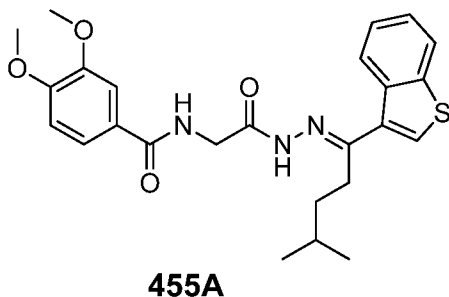
[0466] Compound **452** was obtained following the procedure for obtaining compound **400** using chroman-4-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **452** was obtained as a white solid (100 mg, 45 %). ESI-LCMS: m/z 384 $[M+H]^+$.



[0467] Compound **453** was obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)heptan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **453** was obtained as a white solid (100 mg, 35%). ESI-LCMS: m/z 482 $[M+H]^+$.

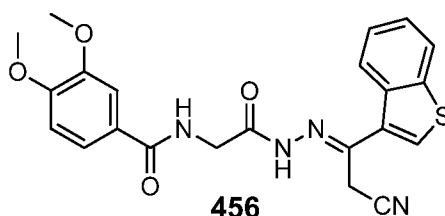


[0468] Compound **454** was obtained following the procedure for obtaining compound **400** using benzoyl cyanide in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **454** was obtained as a white solid (20 mg, 35 %). ESI-LCMS: m/z 367 $[M+H]^+$.

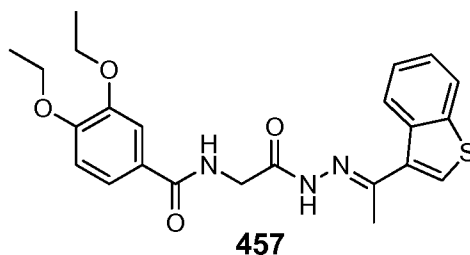


[0469] Compounds **455A** and **455B** were obtained following the procedure for obtaining compound **400** using 1-(benzo[*b*]thiophen-3-yl)-4-methylpentan-1-one in place of

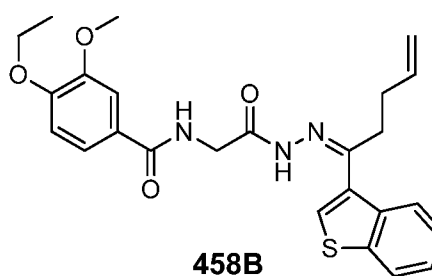
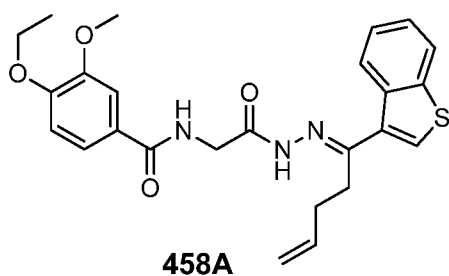
2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **455A** (64 mg, 20.0 %) and Compound **455B** (42 mg, 16.0 %) were obtained as a white solid. Compound **455A**: +ESI-MS: m/z 468.0 $[M+H]^+$. Compound **455B**: +ESI-MS: m/z 468.0 $[M+H]^+$.



[0470] Compound **456** was obtained following the procedure for obtaining compound **400** using 3-(benzo[*b*]thiophen-3-yl)-3-oxopropanenitrile in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **456** was obtained as a white solid (120 mg, 37.25%). +ESI-MS: m/z 458.9 $[M+Na]^+$.

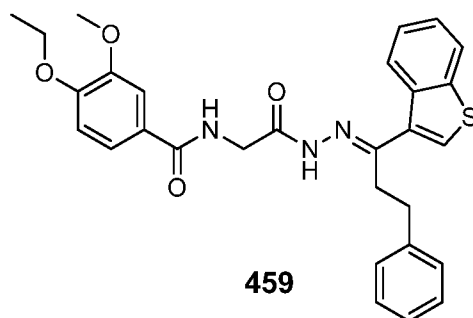


[0471] Compound **457** was obtained following the procedure for obtaining compound **400** using 3,4-diethoxybenzoic acid in place of 3,4-dimethoxybenzoic acid and 1-(1*H*-inden-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **457** was obtained as a white solid (300 mg, 68.3%). +ESI-MS: m/z 439.9 $[M+H]^+$.

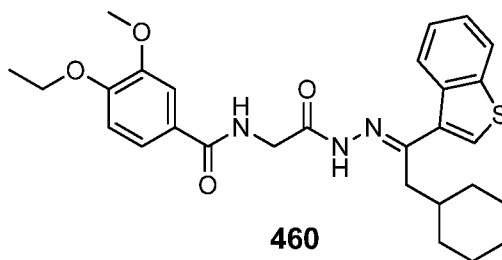


[0472] Compounds **458A** and **458B** were obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxybenzoic acid and 1-benzo[*b*]thiophen-3-yl-pent-4-en-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **458A** (20 mg, 10%) and

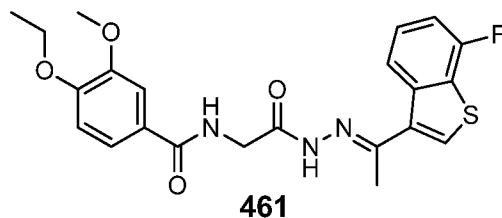
Compound **458B** (2 mg, 1%) were obtained as a white solid. Compound **458A**: +ESI-MS:m/z 465.89 $[M + Na]^+$. Compound **458B**: +ESI-MS:m/z 465.87 $[M + Na]^+$.



[0473] Compound **459** was obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-benzo[*b*]thiophen-3-yl-3-phenyl-propan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **459** was obtained as a white solid (85 mg, 22%). +ESI-MS:m/z 516.1 $[M + H]^+$.

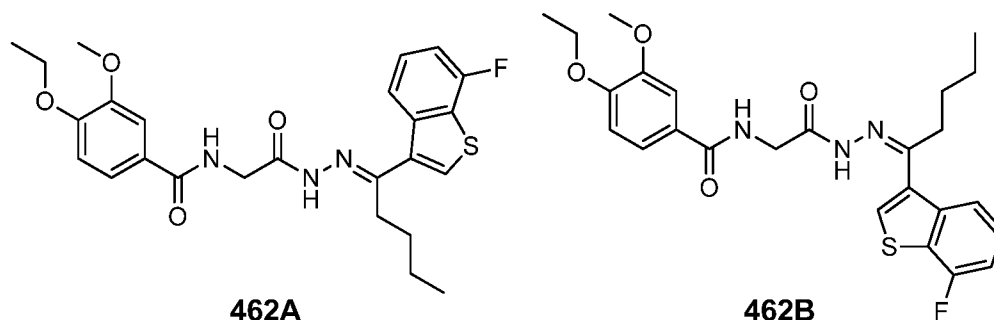


[0474] Compound **460** was obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-benzo[*b*]thiophen-3-yl-2-cyclohexyl-ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **460** was obtained as a white solid (65 mg, 33%). +ESI-MS:m/z 508.1 $[M + H]^+$.

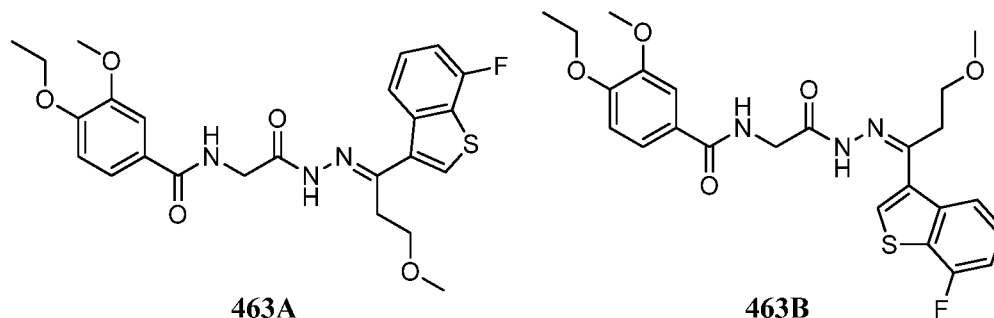


[0475] Compound **461** was obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(7-fluoro-benzo[*b*]thiophen-3-yl)-ethanone in place of 2-

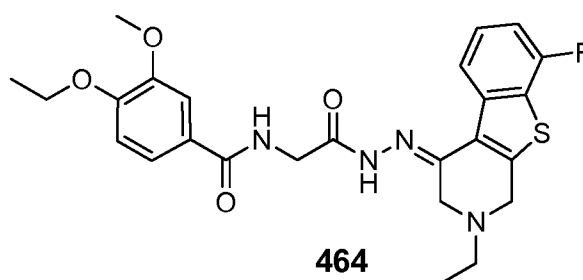
methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **461** was obtained as a white solid (6 mg, yield: 15%). +ESI-MS:*m/z* 443.81 [M+H]⁺.



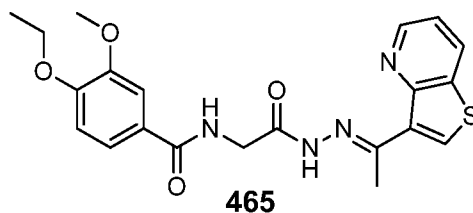
[0476] Compound **462A** and Compound **462B** were obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(7-fluoro-benzo[*b*]thiophen-3-yl)-pentan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **462A** (50 mg, yield: 30.3%) and Compound **462B** (10 mg, yield: 5.9%) were obtained as a white solid. Compound **462A**: +ESI-MS:*m/z* 485.92 [M+H]⁺. Compound **462B**: +ESI-MS:*m/z* 485.91 [M+H]⁺.



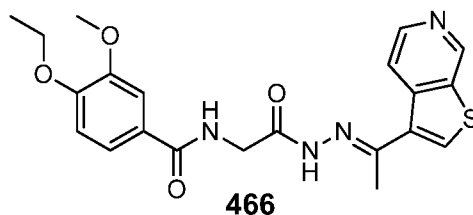
[0477] Compound **463A** and Compound **463B** were obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(7-fluoro-benzo[*b*] thiophen-3-yl)-3-methoxy-propan-1-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **463A** (200 mg, yield: 24.5%) and Compound **463B** (30 mg, yield: 7.6%) were obtained as a white solid. Compound **463A**: +ESI-MS:*m/z* 487.85 [M+H]⁺. Compound **463B**: +ESI-MS:*m/z* 487.87 [M+H]⁺.



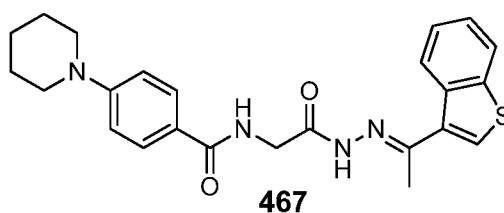
[0478] Compound **464** was obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 2-ethyl-6-fluoro-1,2,3,4-tetrahydro-[1]benzothieno[3,2-c]pyridin-4-one in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **464** was obtained as a white solid (15 mg, 26%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.14 -1.49 (m, 6H), 2.13 -2.34 (m, 2H), 3.70 -3.86 (m, 3H), 4.05 (d, *J* = 7.06 Hz, 3H), 4.51 (br s, 2H), 6.85 -7.15 (m, 3H), 7.23 -7.76 (m, 5H), 8.40 (d, *J* = 7.72 Hz, 1H), 8.63 -8.91 (m, 1H), 11.01 -11.30 (m, 1H).



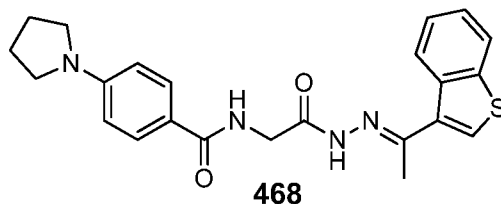
[0479] Compound **465** was obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-thieno[3,2-*b*]pyridin-3-yl-ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **465** was obtained as a white solid (30 mg, yield: 25%). +ESI-MS:*m/z* 427.1 [M+H]⁺.



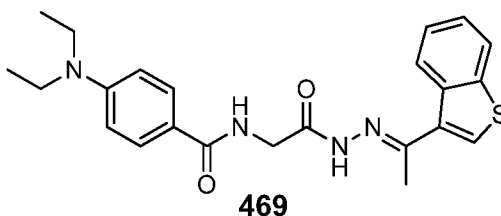
[0480] Compound **466** was obtained following the procedure for obtaining compound **400** using 4-ethoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-thieno[2,3-*c*]pyridin-3-yl-ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **466** was obtained as a white solid (15 mg, yield: 21%). +ESI-MS:*m/z* 427.0 [M+H]⁺.



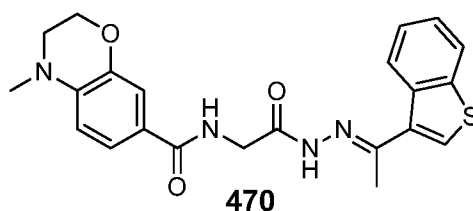
[0481] Compound **467** was obtained following the procedure for obtaining compound **400** using 4-(piperidin-1-yl) benzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **467** was obtained as a white solid (320 mg, 78.2%). +ESI-MS: m/z 435.1 $[M+H]^+$.



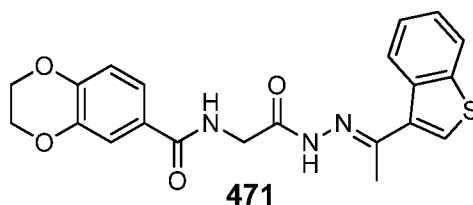
[0482] Compound **468** was obtained following the procedure for obtaining compound **400** using 4-(pyrrolidin-1-yl)benzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **468** was obtained as a white solid (104 mg, 49.9%). +ESI-MS: m/z 421.1 $[M+H]^+$.



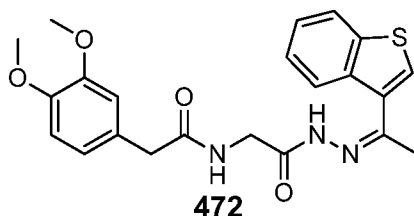
[0483] Compound **469** was obtained following the procedure for obtaining compound **400** using 4-(diethylamino)benzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **469** was obtained as a white solid (120 mg, 50%). +ESI-MS: m/z 423.1 $[M+H]^+$.



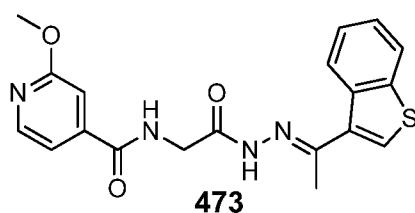
[0484] Compound **470** was obtained following the procedure for obtaining compound **400** using 4-methyl-3,4-dihydro-2H-benzo [b][1,4]oxazine-7-carboxylic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone in place of 2-methylbenzo[b]thiophene-3-carboxaldehyde. Compound **470** was obtained as a white solid (10 mg, 10%). ESI-LCMS: m/z 423 [M+H]⁺.



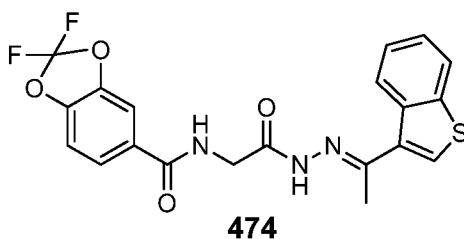
[0485] Compound **471** was obtained following the procedure for obtaining compound **400** using 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone in place of 2-methylbenzo[b]thiophene-3-carboxaldehyde. Compound **471** was obtained as a white solid (50 mg, 43.9%). +ESI-MS:m/z 410.0 [M+H]⁺.



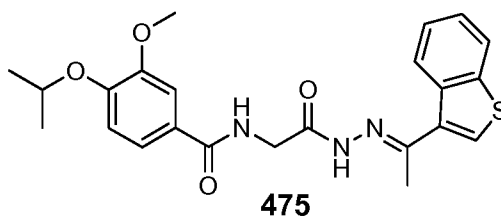
[0486] Compound **472** was obtained following the procedure for obtaining compound **400** using 2-(3,4-dimethoxyphenyl)acetic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone in place of 2-methylbenzo[b]thiophene-3-carboxaldehyde. Compound **472** was obtained as a white solid (60 mg, 24.5%). +ESI-LCMS: m/z 426 [M+H]⁺.



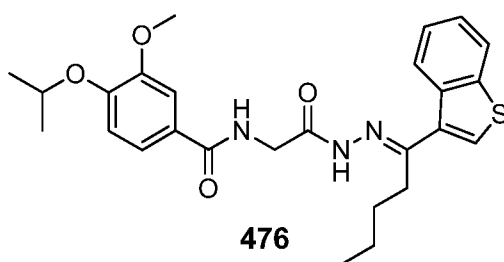
[0487] Compound **473** was obtained following the procedure for obtaining compound **400** using 2-methoxyisonicotinic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **473** was obtained as a white solid (60 mg, 18%). +ESI-LCMS: m/z 383 $[M+H]^+$.



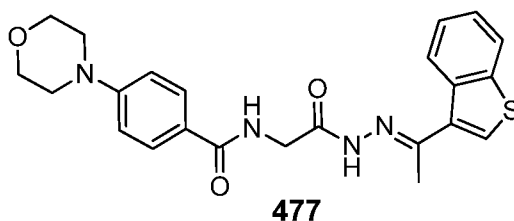
[0488] Compound **474** was obtained following the procedure for obtaining compound **400** using 2,2-difluorobenzo[*d*][1,3]dioxole-5-carboxylic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **474** was obtained as a white solid (100 mg, 57.80%). +ESI-MS: m/z 432.0 $[M+H]^+$.



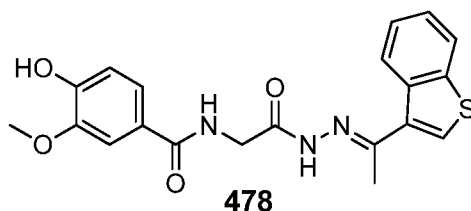
[0489] Compound **475** was obtained following the procedure for obtaining compound **400** using 4-isopropoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **475** was obtained as a white solid (75 mg, 60.0%). +ESI-MS: m/z 440.0 $[M+H]^+$.



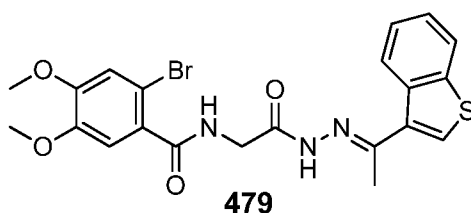
[0490] Compound **476** was obtained following the procedure for obtaining compound **400** using 4-isopropoxy-3-methoxybenzoic acid in place of 3,4-dimethoxybenzoic acid and 1-(benzo[b]thiophen-3-yl)pentan-1-one in place of benzo[b]thiophene-3-carbaldehyde. Compound **476** was obtained as a white solid (142 mg, 57.0%). +ESI-MS: m/z 481.9 $[M+H]^+$.



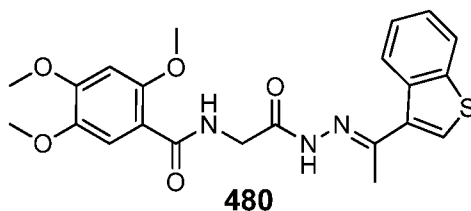
[0491] Compound **477** was obtained following the procedure for obtaining compound **400** using 4-morpholin-4-ylbenzoic acid in place of 3,4-dimethoxybenzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone in place of 2-methylbenzo[b]thiophene-3-carboxaldehyde. Compound **477** was obtained as a white solid (60 mg, 13%). ESI-LCMS: m/z 383 $[M+H]^+$.



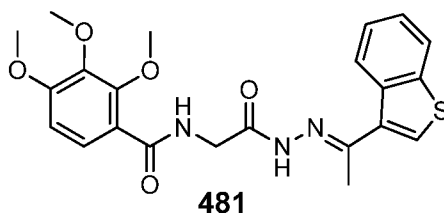
[0492] Compound **478** was obtained following the procedure for obtaining compound **400** using 4-hydroxy-3-methoxybenzoic acid in place of 3,4-dimethoxybenzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone in place of 2-methylbenzo[b]thiophene-3-carboxaldehyde. Compound **478** was obtained as a white solid (40 mg, 13%). +ESI-LCMS: m/z 398 $[M+H]^+$.



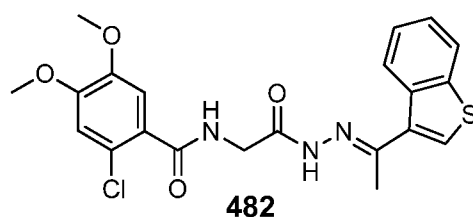
[0493] Compound **479** was obtained following the procedure for obtaining compound **400** using 2-bromo-4,5-dimethoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **479** was obtained as a white solid (80 mg, 13%). +ESI-LCMS: m/z 492 $[M+H]^+$.



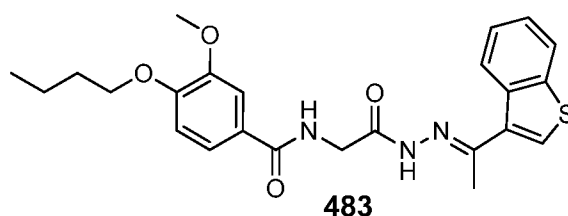
[0494] Compound **480** was obtained following the procedure for obtaining compound **400** using 2,4,5-trimethoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **480** was obtained as a white solid (30 mg, 13%). ESI-LCMS: m/z 442 $[M+H]^+$.



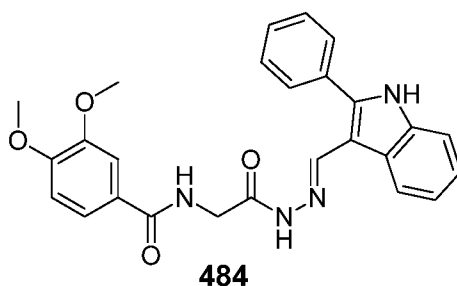
[0495] Compound **481** was obtained following the procedure for obtaining compound **400** using 2,3,4-trimethoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[*b*]thiophen-3-yl)ethanone in place of 2-methylbenzo[*b*]thiophene-3-carboxaldehyde. Compound **481** was obtained as a white solid (180 mg, 57.88 %). +ESI-MS: m/z 442.1 $[M+H]^+$.



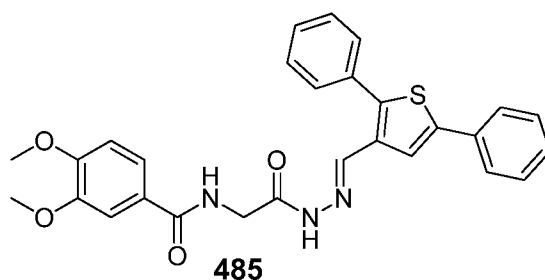
[0496] Compound **482** was obtained following the procedure for obtaining compound **400** using 2-chloro-4,5-dimethoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone in place of 2-methylbenzo[b]thiophene-3-carboxaldehyde. Compound **482** was obtained as a white solid (125 mg, 98.4%). +ESI-MS:m/z 446.0 [M+H]⁺.



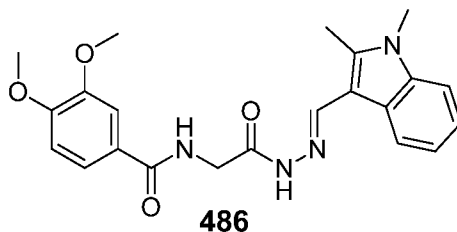
[0497] Compound **483** was obtained following the procedure for obtaining compound **400** using 4-butoxy-3-methoxybenzoic acid in place of 3,4-dimethoxy-benzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone in place of 2-methylbenzo[b]thiophene-3-carboxaldehyde. Compound **483** was obtained as a white solid (120 mg, 35.60%). +ESI-MS:m/z 454.3[M+H]⁺.



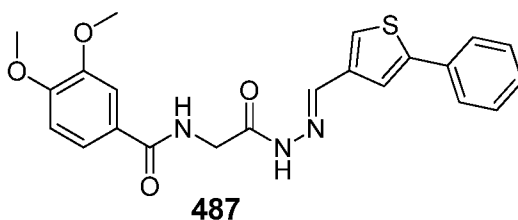
[0498] Compound **484** was obtained essentially following the procedure for obtaining compound **400** using N-(2-hydrazinyl-2-oxoethyl)-3,4-dimethoxybenzamide and 2-phenyl-1H-indole-3-carbaldehyde as the starting materials. Compound **484** was obtained as a white solid. +ESI-MS: m/z 457.0 [M +H]⁺.



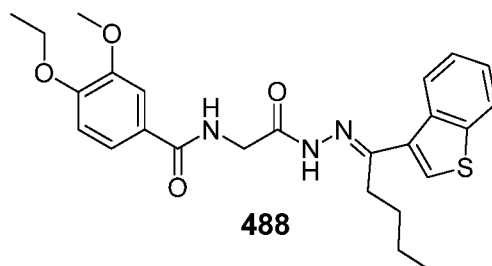
[0499] Compound **485** was obtained essentially following the procedure for obtaining compound **400** using N-(2-hydrazinyl-2-oxoethyl)-3,4-dimethoxybenzamide and 2,5-diphenylthiophene-3-carbaldehyde as the starting materials. Compound **485** was obtained as a white solid. +ESI-MS: m/z 500.1 [M + H]⁺.



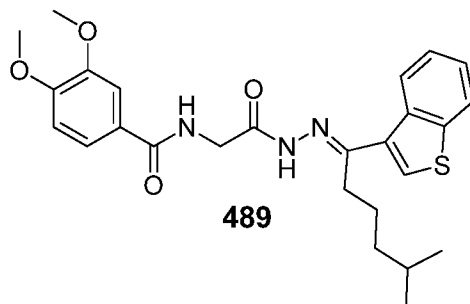
[0500] Compound **486** was obtained essentially following the procedure for obtaining compound **400** using 1,2-dimethyl-1H-indole-3-carbaldehyde as the starting material. Compound **486** was obtained as a white solid. +ESI-MS: m/z 409.1 [M + H]⁺.



[0501] Compound **487** was obtained essentially following the procedure for obtaining compound **400** using N-(2-hydrazinyl-2-oxoethyl)-3,4-dimethoxybenzamide and 5-phenylthiophene-3-carbaldehyde as the starting materials. Compound **487** was obtained as a white solid. +ESI-MS: m/z 424.1 [M + H]⁺.

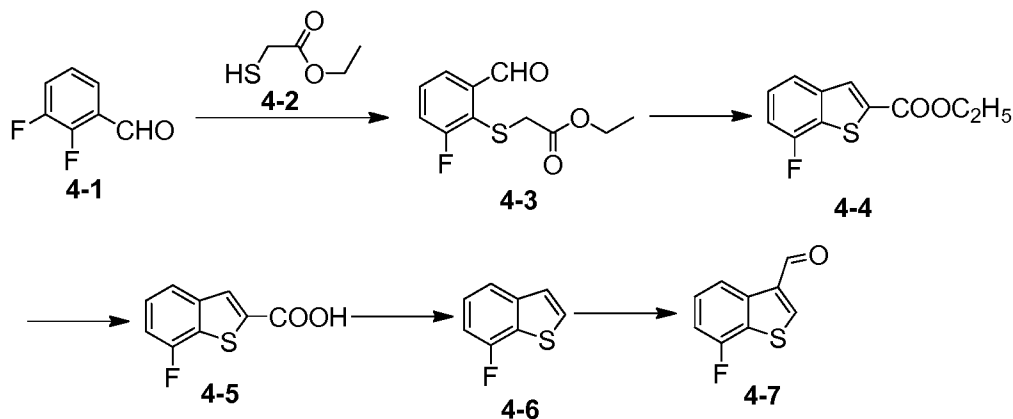


[0502] Compound **488** was obtained essentially following the procedure for obtaining compound **400** using 4-ethoxy-N-(2-hydrazinyl-2-oxoethyl)-3-methoxybenzamide and 1-(benzo[b]thiophen-3-yl)pentan-1-one as the starting materials. Compound **488** was obtained as a white solid. +ESI-MS: m/z 468.1 $[M + H]^+$.



[0503] Compound **489** was obtained essentially following the procedure for obtaining compound **400**. Compound **489** was obtained as a white solid (100 mg, 35%). +ESI-MS: m/z 482.0 $[M + H]^+$.

EXAMPLE 4-1 **Preparation of Compound 4-7**



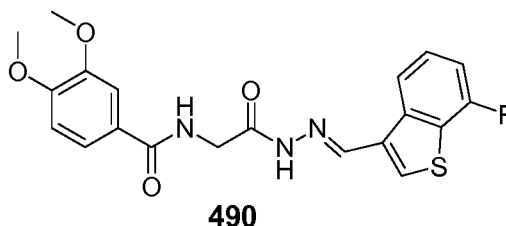
[0504] To a solution of **4-1** (48 g, 0.34 mmol) and K_2CO_3 (60 g, 0.5 mmol) at $0^\circ C$ in DMF (200 mL) was added **4-2** (44 g, 0.37 mmol). The mixture was stirred at rt for 12 h, and then heated at $70^\circ C$ for 5 h. After cooling to rt, the mixture was poured into water, and extracted with EA. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to give **4-4** (75 g, 80.5 %).

[0505] A mixture of **4-4** (75 g, 335 mmol), KOH (93 g, 1.66 mol), H_2O (500 mL) and EtOH (500 mL) was refluxed for 2 h. The mixture was concentrated, acidified to pH=3

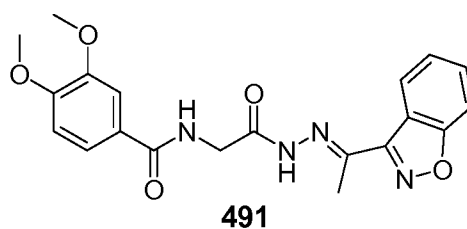
with 2N HCl solution and then extracted with EA. The combined organic layer was dried over sodium sulfate and concentrated to give **4-5** (60 g, 88 %).

[0506] To a solution of **4-5** (4 g, 20.4 mmol) in quinoline (21 mL) was added Cu powder (440 mg, 6.12 mmol) at rt. The mixture was heated to 185°C and stirred for 2 h. The solution was cooled to rt, poured into 2N HCl solution and extracted with DCM. The organic phase was concentrated (< 40°C) to give crude **4-6** (3.3g, 74.2%).

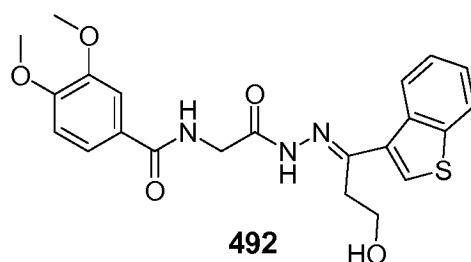
[0507] Compound **4-6** (12 g, 79 mmol) and dichloromethyl methyl ether (13.5, 118 mmol) were dissolved in anhydrous DCM (400 mL). To the solution was added titanium tetrachloride (23 g, 122 mmol). After stirring at rt for 1 h, the mixture was poured into a mixture of saturated aqueous NaHCO₃ and ice. The mixture was stirred for about 30 mins and then extracted with DCM. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatograph on silica gel (PE:EA=80:1 to 20:1) to give **4-7** (6.0 g, 40 %). ¹H-NMR (400MHz, *d*-DMSO), δ=10.14 (d, J=1.0 Hz, 1 H), 9.05 (s, 1 H), 8.36-8.34 (m, 1 H), 7.60-7.55 (m, 1 H), 7.41-7.37 (m, 1 H).



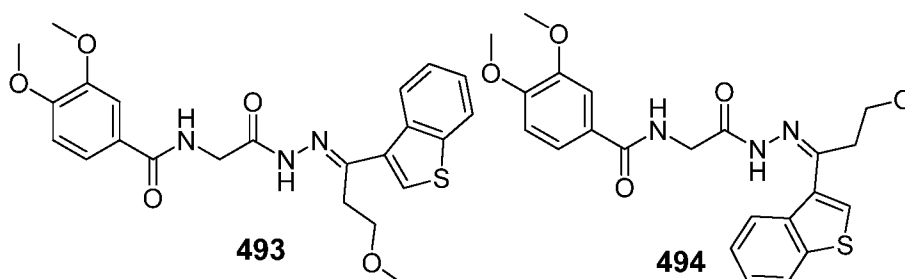
[0508] Compound **490** was obtained essentially following the procedure for obtaining compound **400** using **4-7** as the starting material. Compound **490** was obtained as a white solid (20 mg, 43,8%). +ESI-MS: *m/z* 416.2 [M +H]⁺.



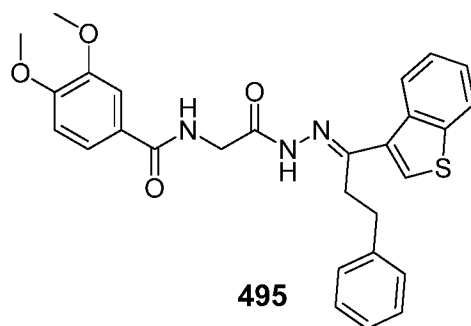
[0509] Compound **491** was obtained essentially following the procedure for obtaining compound **400**. Compound **491** was obtained as a white solid (50 mg, 61.5%). +ESI-MS: *m/z* 397.0 [M +H]⁺.



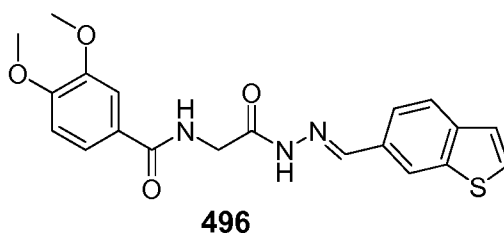
[0510] Compound **492** was obtained essentially following the procedure for obtaining compound **400**. Compound **492** was obtained as a white solid (10 mg, 20%). +ESI-MS: m/z 442.0 $[M + H]^+$.



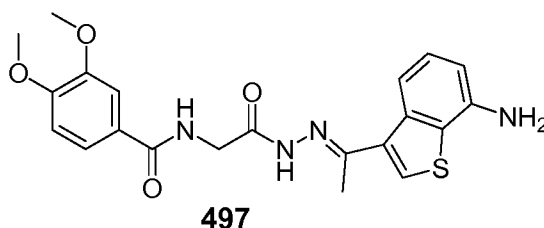
[0511] Compounds **493** and **494** were obtained essentially following the procedure for obtaining compound **400**. Compounds **493** (18 mg, 40.1%) and compound **494** (8 mg, 18.5%) were obtained as a white solid. Compound **493**: +ESI-MS: m/z 456.0 $[M + H]^+$. Compound **494**: +ESI-MS: m/z 456.1 $[M + H]^+$.



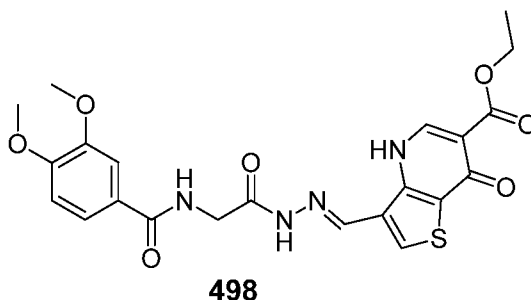
[0512] Compound **495** was obtained essentially following the procedure for obtaining compound **400**. Compound **495** was obtained as a white solid (95 mg, 25.20%). +ESI-MS: m/z 502.1 $[M + H]^+$.



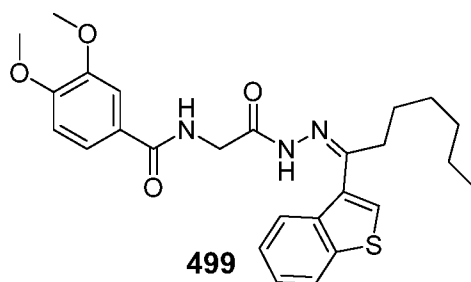
[0513] Compound **496** was obtained essentially following the procedure for obtaining compound **400**. Compound **496** was obtained as a white solid (20 mg, 50%). +ESI-MS: m/z 398.0 $[M + H]^+$.



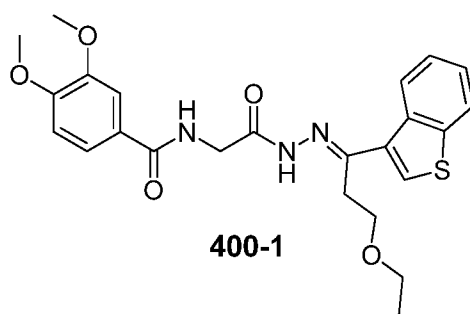
[0514] Compound **497** was obtained essentially following the procedure for obtaining compound **400**. Compound **497** was obtained as a white solid (30 mg, 30%). +ESI-MS: m/z 427.0 $[M + H]^+$.



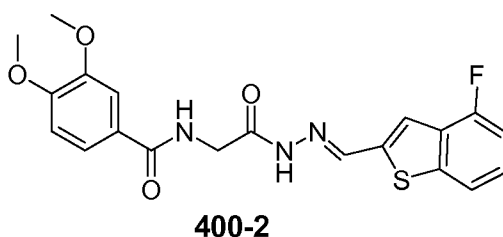
[0515] Compound **498** was obtained essentially following the procedure for obtaining compound **400**. Compound **498** was obtained as a white solid (25 mg, 43.1%). +ESI-MS: m/z 487.0 $[M + H]^+$.



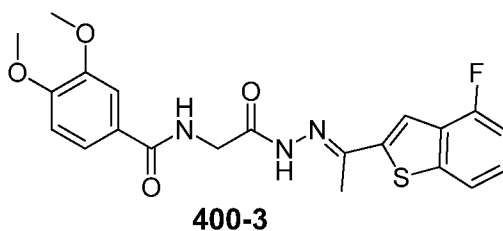
[0516] Compound **499** was obtained essentially following the procedure for obtaining compound **400**. Compound **499** was obtained as a white solid (80 mg, 35.5%). +ESI-MS: m/z 482.1 $[M + H]^+$.



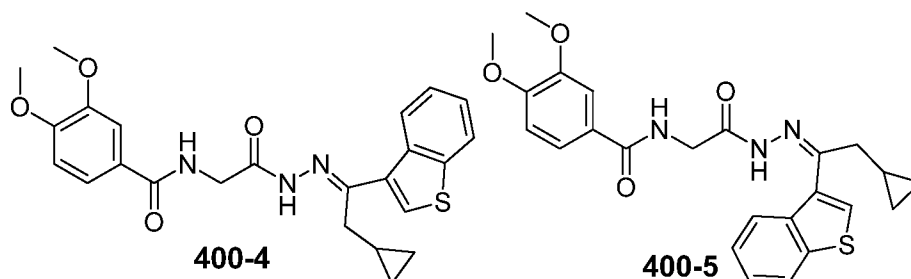
[0517] Compound **400-1** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-1** was obtained as a white solid (15 mg, 38.46%). +ESI-MS: m/z 470.0 $[M + H]^+$.



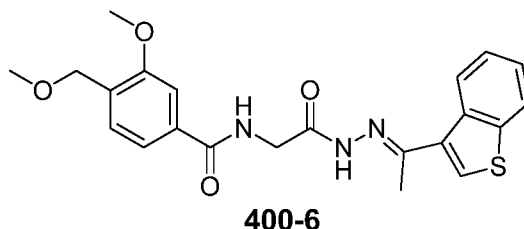
[0518] Compound **400-2** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-2** was obtained as a white solid (115 mg, 62.5%). +ESI-MS: m/z 416.0 $[M + H]^+$.



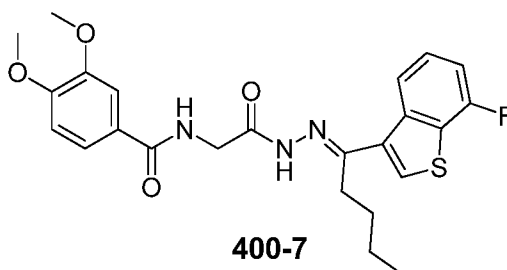
[0519] Compound **400-3** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-3** was obtained as a white solid (124 mg, 56.9%). +ESI-MS: m/z 430.0 $[M + H]^+$.



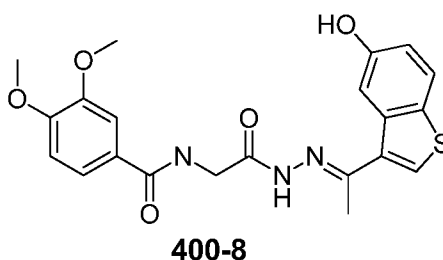
[0520] Compounds **400-4** and **400-5** were obtained essentially following the procedure for obtaining compound **400**. Compounds **400-4** (101 mg, 27.7%) and compound **400-5** (319 mg, 81.8%) were obtained as a white solid. Compound **400-4**: +ESI-MS: m/z 452.0 $[M + H]^+$. Compound **400-5**: +ESI-MS: m/z 452.1 $[M + H]^+$.



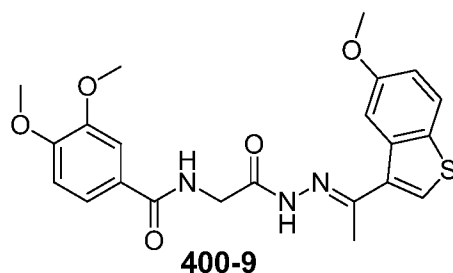
[0521] Compound **400-6** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-6** was obtained as a white solid (60 mg, 10.2%). +ESI-MS: m/z 426.1 $[M + H]^+$.



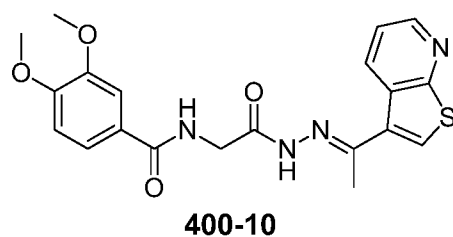
[0522] Compound **400-7** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-7** was obtained as a white solid (20 mg, 20.2%). +ESI-MS: m/z 471.89 $[M + H]^+$.



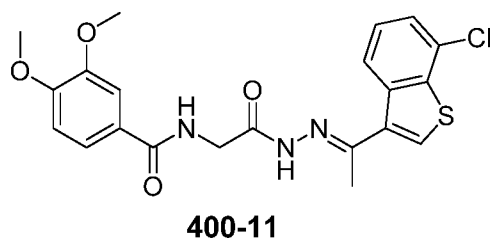
[0523] Compound **400-8** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-8** was obtained as a white solid (39 mg, 57.4%). +ESI-MS: m/z 428.0 $[M + H]^+$.



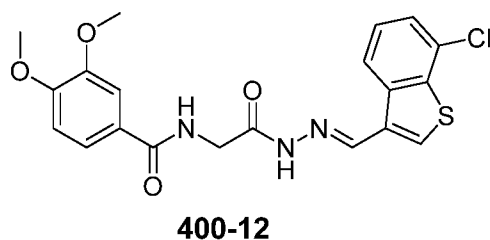
[0524] Compound **400-9** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-9** was obtained as a white solid (76 mg, 52.4%). +ESI-MS: m/z 442.0 $[M + H]^+$.



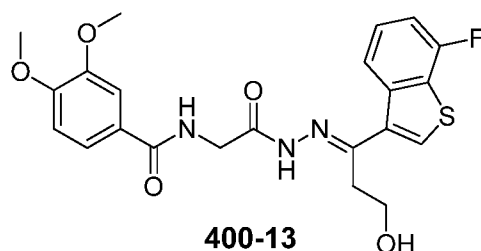
[0525] Compound **400-10** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-10** was obtained as a white solid (40 mg, 21.6%). +ESI-MS: m/z 413.0 $[M + H]^+$.



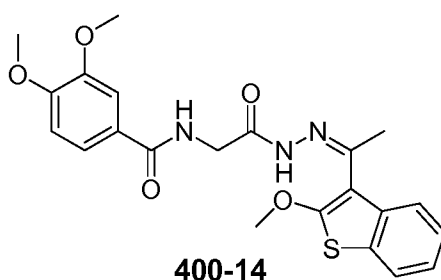
[0526] Compound **400-11** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-11** was obtained as a white solid (28 mg, 13.5%). +ESI-MS: m/z 445.8 $[M + H]^+$.



[0527] Compound **400-12** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-12** was obtained as a white solid (115 mg, 58.1%). +ESI-MS: m/z 432.0 $[M + H]^+$.

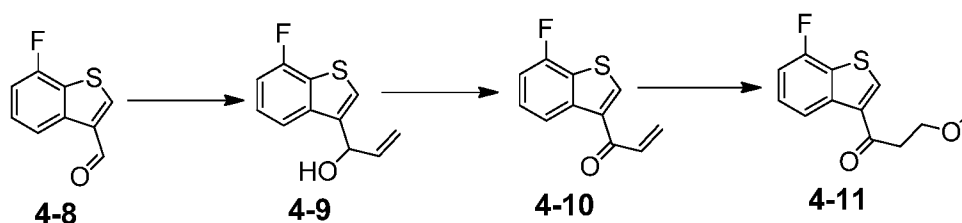


[0528] Compound **400-13** was obtained essentially following the procedure for obtaining compound **400** by using N-(2-hydrazinyl-2-oxoethyl)-3,4-dimethoxybenzamide and 1-(7-fluorobenzo[b]thiophen-3-yl)-3-hydroxypropan-1-one as the starting materials. Compound **400-13** was obtained as a white solid. +ESI-MS: m/z 460.1 [M + H]⁺.



[0529] Compound **400-14** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-14** was obtained as a white solid (4 mg, 8.2%). +ESI-MS: m/z 442.0 [M + H]⁺.

EXAMPLE 4-2 **Preparation of Compound 4-11**

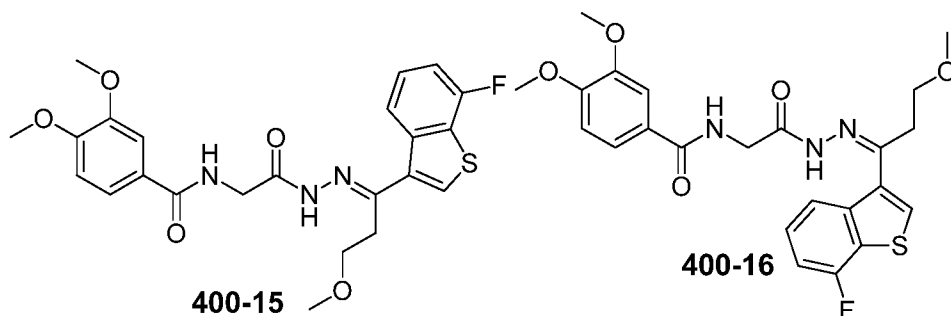


[0530] To a solution of **4-8** (10.0 g, 55.6 mmol) in anhydrous THF (250 mL) was added vinylmagnesium chloride (61 mL, 1.0 M THF) dropwise under a nitrogen atmosphere at 0°C. The mixture was stirred at rt for 2 h with TLC monitoring. The reaction was quenched by addition of aq. NH₄Cl and extracted by EA. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give crude **4-9** (10.5 g, 80 %).

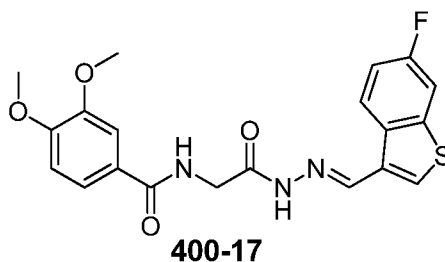
[0531] To a solution of **4-9** (10.5 g, 50.5 mmol) in anhydrous DCM (200 mL) was add MnO₂ (39 g, 450 mmol). The mixture was stirred at 40°C for 10 h with TLC monitoring. The mixture was filtered through a 2-cm Celite filter pad and the pad was

washed with DCM (100 mL). The clear filtrate was concentrated. The residue was purified by column chromatography on silica gel (PE/EA=20:1-5:1) to give **4-10** (9.0 g, 70%).

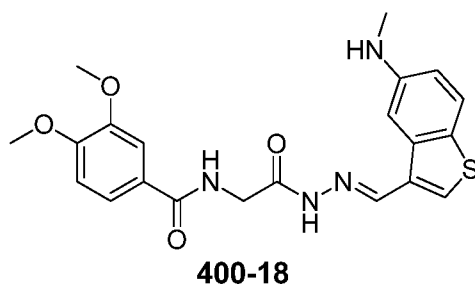
[0532] To a solution of **4-10** (6.5 g, 31.6 mmol) in anhydrous MeOH (80 mL) was added DBU (0.49 g, 3.2 mmol). The mixture was stirred at 40°C for 3 h with TLC monitoring. The reaction was quenched with aq. NH₄Cl, and extracted by EA. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated at low pressure. The residue was purified by column chromatography on silica gel (PE/EA=10:1 to 5:1) to give **4-11** (5.0 g, 60 %). ¹H-NMR (*d*-DMSO, 400MHz), δ =9.08 (s, 1 H), 8.43 (d, *J*=8.1 Hz, 1 H), 7.57-7.52 (m, 1H), 7.38-7.33 (m, 1 H), 3.74-3.71 (m, 2 H), 3.30-3.27 (m, 2 H), 3.25 (s, 3 H).



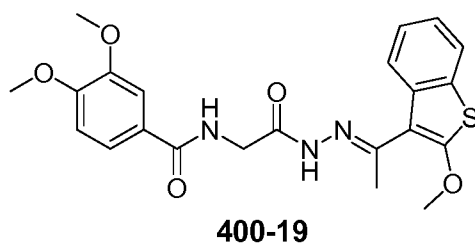
[0533] Compounds **400-15** and **400-16** were obtained essentially following the procedure for obtaining compound **400** using **4-11** as the starting material. Compounds **400-15** (50 mg, 30%) and compound **400-16** (5 mg, 3%) were obtained as a white solid. Compound **400-15**: +ESI-MS: *m/z* 473.8 [M + H]⁺. Compound **400-16**: +ESI-MS: *m/z* 473.9 [M + H]⁺.



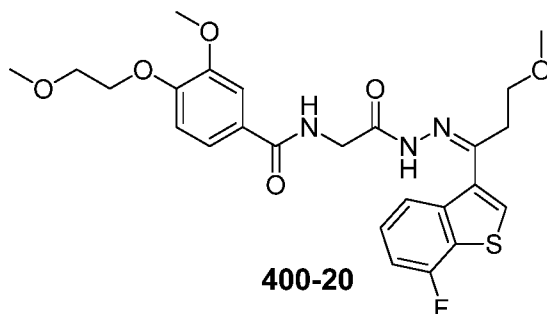
[0534] Compound **400-17** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-17** was obtained as a white solid (40 mg, 34.8%). +ESI-MS: *m/z* 415.9 [M + H]⁺.



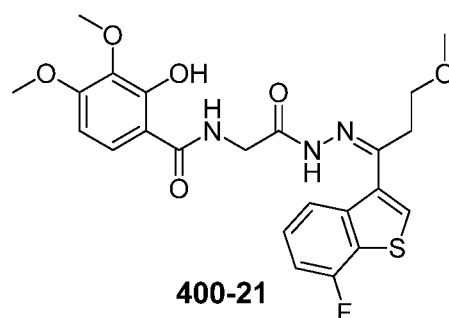
[0535] Compound **400-18** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-18** was obtained as a white solid (20 mg, 15.0%). +ESI-MS: m/z 427.2 $[M + H]^+$.



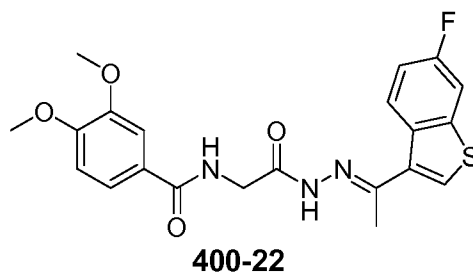
[0536] Compound **400-19** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-19** was obtained as a white solid (12 mg, 12.4%). +ESI-MS: m/z 442.0 $[M + H]^+$.



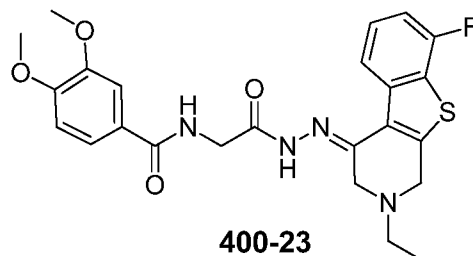
[0537] Compound **400-20** was obtained essentially following the procedure for obtaining compound **400** using 4-hydroxy-3-methoxy-benzoic acid ethyl ester as the starting material. Compound **400-20** was obtained as a white solid (110 mg, 50.8%). +ESI-MS: m/z 518.0 $[M + H]^+$.



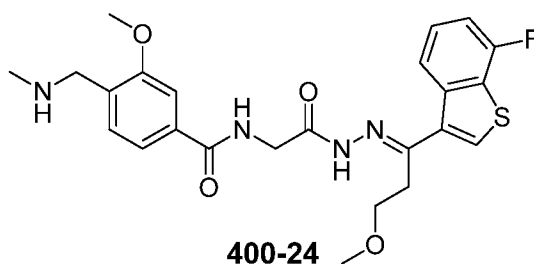
[0538] Compound **400-21** was obtained essentially following the procedure for obtaining compound **400** using **4-11** as the starting material. Compound **400-21** was obtained as a white solid (110 mg, 50.8%). +ESI-MS: m/z 490.1 $[M + H]^+$.



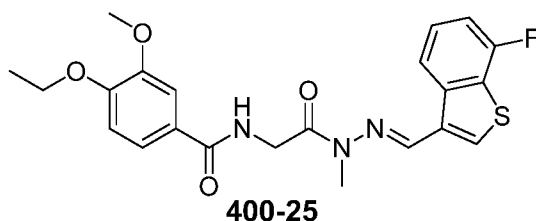
[0539] Compound **400-22** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-22** was obtained as a white solid (126 mg, 57.3%). +ESI-MS: m/z 430.1 $[M + H]^+$.



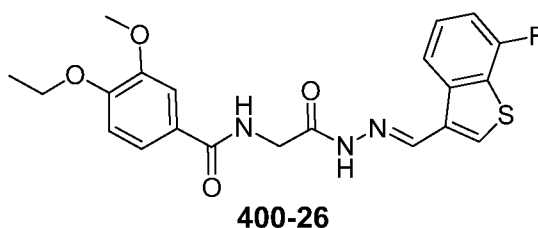
[0540] Compound **400-23** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-23** was obtained as a white solid (15 mg, 35.2%). +ESI-MS: m/z 485.2 $[M + H]^+$.



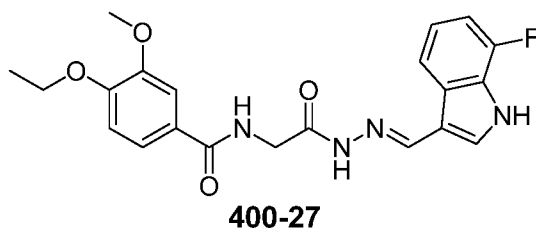
[0541] Compound **400-24** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-24** was obtained as a white solid (2 mg). +ESI-MS: m/z 487.1 [M+H]⁺.



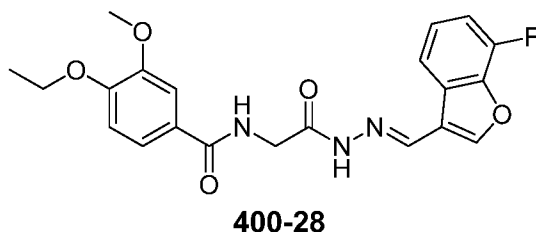
[0542] Compound **400-25** was obtained essentially following the procedure for obtaining compound **400**. Compound **400-25** was obtained as a white solid. +ESI-MS: m/z 444.0 $[M + H]^+$.



[0543] Compound **400-26** was obtained essentially following the procedure for obtaining compound **400** using 7-fluorobenzo[b]thiophene-3-carbaldehyde as starting material. Compound **400-26** was obtained as a white solid (50 mg, 15.0%). +ESI-MS: m/z 430.0 $[M+H]^+$.

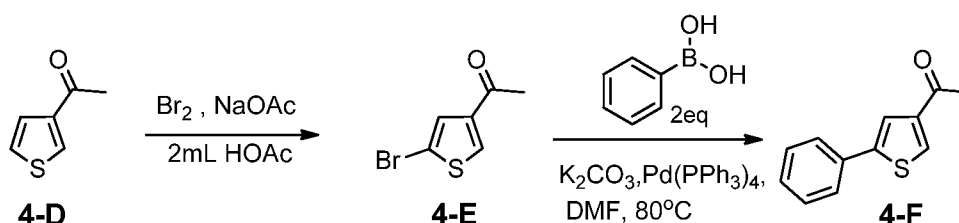


[0544] Compound **400-27** was obtained essentially following the procedure for obtaining compound **400** using 7-fluoro-1H-indole-3-carbaldehyde. Compound **400-27** was obtained as a white solid (40 mg, 16.0%). +ESI-MS: m/z 413.0 [M + H]⁺.



[0545] Compound **400-28** was obtained essentially following the procedure for obtaining compound **400** using 7-fluoro-1H-indole-3-carbaldehyde. Compound **400-28** was obtained as a white solid (60 mg, 18.0%). +ESI-MS: m/z 414.0 $[M + H]^+$.

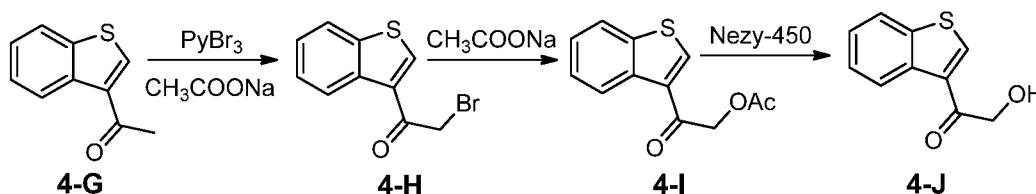
EXAMPLE 4-3
Preparation of Compound 4-F



[0546] To a solution of 2-acetylthiophene (**4-D**) (0.4 g, 3.17 mmol) in HOAc (5 mL), NaOAc (0.29 g, 3.5 mmol) was added at rt. The solution was stirred for 10 mins at rt. Then Br₂ (0.508 g, 3.17 mmol) was added dropwise at 0°C. The solution was stirred for 2 h. The solution was neutralized with NaHCO₃ aqueous and extracted with EA. The organic phase was concentrated to afford crude 4-acetyl-2-bromothiophene (**4-E**) (0.4 g, 61.5 %).

[0547] To a solution of 4-acetyl-2-bromothiophene (**4-E**) (0.4 g, 1.95 mmol) in DMF (10 mL), phenylboronic acid (0.285 g, 2.34 mmol), Pd(PPh₃)₄ (0.225 g, 0.195 mmol) and K₂CO₃ (0.53 g, 3.9 mmol) were added at rt under N₂ atmosphere. The mixture was stirred for 15 h at 80-90°C. The solution was poured into water and extracted with EA. The organic phase was concentrated and the residue was purified by silica gel chromatography with (PE) to afford 1-(5-phenylthiophen-3-yl)ethanone (**4-F**) (100 mg, 25.3 %).

EXAMPLE 4-4
Preparation of Compound 4-J

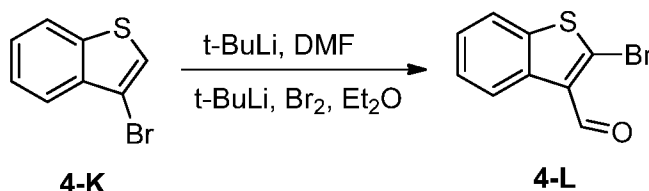


[0548] To a solution of 1-(benzo[*b*]thiophen-3-yl)ethanone (**4-G**) (1.63 g, 10.0 mmol) in CH₃CN (60 mL) was added PyBr₃ (3.19 g, 10 mmol) and CH₃COONa (820 mg, 10.0 mmol), the mixture was stirred at 80°C overnight. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **4-H** as a white solid (1.3 g, 50.9%).

[0549] To a solution of **4-H** (1.27 g, 5.0 mmol) in CH₃CN (60 mL) was added CH₃COONa (820 mg, 10.0 mmol), the mixture was stirred at 80°C overnight. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **4-I** as a white solid (900 mg, 81.4%).

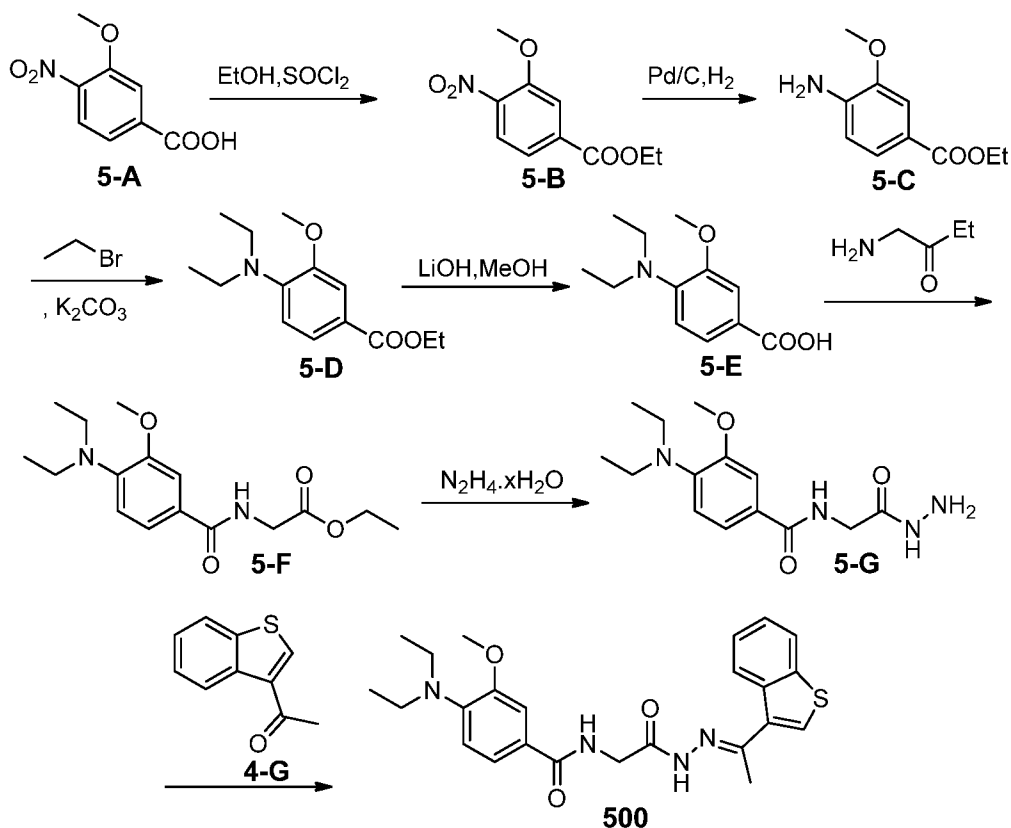
[0550] To a solution of **4-I** (900 mg, 3.85 mmol) in CH₃CN (60 mL) was added Nezy-450 (200 mg), the mixture was stirred at 80°C overnight. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **4-J** as a white solid (480 mg, 64.9%).

EXAMPLE 4-5
Preparation of Compound 4-L



[0551] To a solution of 3-bromobenzo[*b*]thiophene (**4-K**) (4 g, 18.7 mmol) in Et₂O (20 mL), *t*-BuLi (15.6 mL, 1.3M in hexane) was added at –78°C. The solution was stirred for 30 mins at –78°C and DMF (1.5 g, 20.6 mmol) was then added. The cooling bath was removed and the mixture was stirred for another 30 mins at rt. The mixture was cooled to –30°C. Another portion of *t*-BuLi (15.6 mL, 1.3 M in hexane) was added at –30°C. The cooling bath was removed and the mixture was stirred for another 30 mins at rt. The mixture was cooled to –78°C. And a solution of bromine (3.9 g, 24.4 mmol) in hexane was in one portion. The temperature was allowed to gradually rise to 0°C (2 h). The solution was diluted with 1M HCl and extracted with EA. The organic phase was concentrated and the residue was purified by chromatography with silica gel to afford the 2-bromobenzo[*b*]thiophene-3-carboxaldehyde (**4-L**) (0.3 g, 7 %).

EXAMPLE 5
Preparation of Compound 500



[0552] To a solution of 3-methoxy-4-nitrobenzoic acid (**5-A**) (7.00 g, 35.5 mmol) in EtOH (40 mL) was added SOCl₂ (7 mL). The mixture was stirred for 60°C for 14 h. The mixture was concentrated to afford crude ethyl 3-methoxy-4-nitrobenzoate (**5-B**) (7.650 g).

[0553] To a solution of ethyl 3-methoxy-4-nitrobenzoate (**5-B**) (7.65 g, 34 mmol) in EtOH (20 mL) was added Pd/C (1.5 g), while stirring at rt under H₂ for 12 h. The solid was removed by filtration and the mixture was extracted with EA. The solvent was removed to afford ethyl 4-amino-3-methoxybenzoate (**5-C**) (7.5 g).

[0554] Ethyl 4-amino-3-methoxybenzoate (**5-C**) (3 g, 15.37 mmol) was dissolved in MeCN (10 mL), K₂CO₃ (5.310 g, 38.43 mmol) and ethyl bromide (3.350 g, 30.73 mmol) were added. The solution was stirred at 100°C for 24 h in a 30 mL of autoclave. The mixture was filtered and the filtrate was concentrated to afford ethyl 4-(diethylamino)-3-methoxybenzoate (**5-D**) (392 mg).

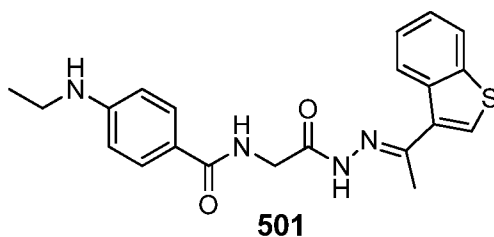
[0555] To a solution of ethyl 4-(diethylamino)-3-methoxybenzoate (**5-D**) (392 mg, 1.56 mmol) in THF (2 mL) and H₂O (2 mL) were added LiOH (391.5 mg, 9.33 mmol)

and MeOH (2 mL). The mixture was stirred at 40°C for 2 h. The mixture solution was concentrate and the remaining mixture was dissolved in EA/HCl, then filtered. The filtrate was concentrated to afford 4-(diethylamino)-3-methoxybenzoic acid (**5-E**) (300 mg, 87%).

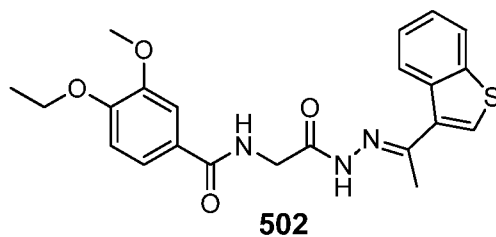
[0556] To a solution of 4-(diethylamino)-3-methoxybenzoic acid (**5-E**) (300 mg, 1.34 mmol) in DCM (10 mL) was added HATU (1.02 g, 2.7 mmol) and DIPEA (433 mg, 3.4 mmol), the mixture was stirred at rt for 30 mins, then ethyl 2-aminoacetate (187 g, 1.34 mmol) was added. The mixture was stirred at rt for another 15 h. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **5-F** as a white solid (385 mg, 93%).

[0557] To a solution of **5-F** (385 mg, 1.25 mmol) in anhydrous ethanol (10 mL) was added $\text{N}_2\text{H}_4 \cdot x\text{H}_2\text{O}$ (520 mg, 16.2 mmol), the mixture was stirred at 100°C for 4 h. Then the mixture was allowed to cool to rt and a white precipitate was formed. The precipitate was filtered and washed with EtOH (20 mL) to afford **5-G** as a white product (321 mg, 87%).

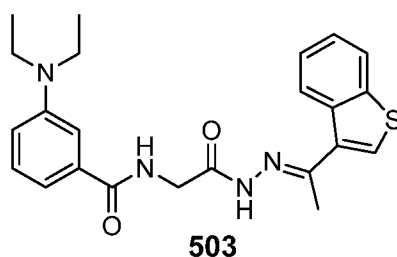
[0558] Compound **5-G** (100 mg, 0.34 mmol) was dissolved in anhydrous EtOH (5 mL). To this solution were added 1-Benzo[*b*]thiophene-3-yl-ethanone (**4-G**) (60 mg, 0.34 mmol) and AcOH (0.4 mL). The mixture was stirred at 60°C for 10 h. The mixture was filtered, and the residue was washed with EtOH (10 mL) and EA (10 mL) to afford compound **500** (40 mg, 26.14%). +ESI-MS: m/z 453.0 $[\text{M}+\text{H}]^+$.



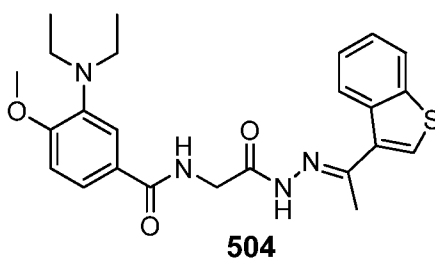
[0559] Compound **501** was obtained following the procedure for obtaining compound **500** using 4-nitrobenzoic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **501** was obtained as a white solid (56 mg, 21%). +ESI-MS: m/z 395.0 $[\text{M}+\text{H}]^+$.



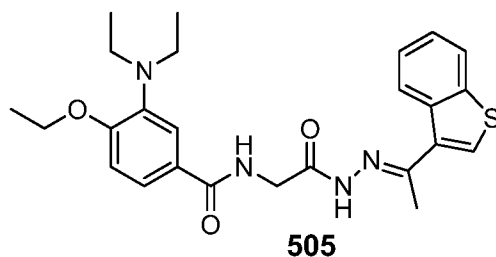
[0560] Compound **502** was obtained following the procedure for obtaining compound **500** using 4-hydroxy-3-methoxybenzoic acid in place of ethyl 4-amino-3-methoxybenzoate. Compound **502** was obtained as a white solid (75 mg, 62.0%). +ESI-MS:m/z 426.1 [M+H]⁺.



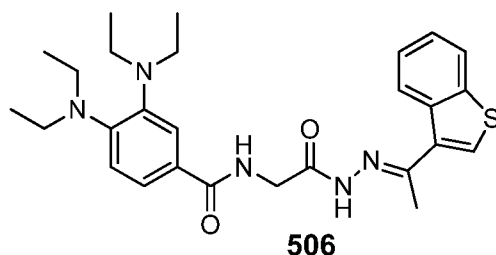
[0561] Compound **503** was obtained following the procedure for obtaining compound **500** using 3-nitrobenzoic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **503** was obtained as a white solid (15 mg, 31.25%). +ESI-MS:m/z 423.1.



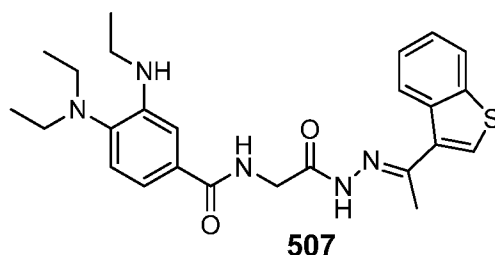
[0562] Compound **504** was obtained following the procedure for obtaining compound **500** using 4-methoxy-3-nitrobenzoic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **504** was obtained as a white solid (75 mg, 58%). +ESI-MS:m/z 453.1 [M+H]⁺.



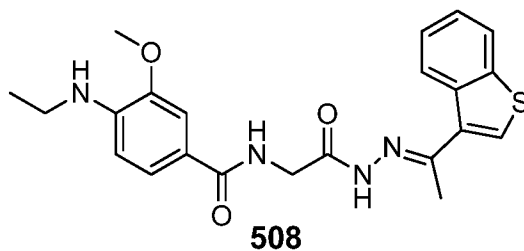
[0563] Compound **505** was obtained following the procedure for obtaining compound **500** using 4-hydroxy-3-nitrobenzoic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **505** was obtained as a white solid (68 mg, 52%). +ESI-MS:m/z 467.1 [M+H]⁺.



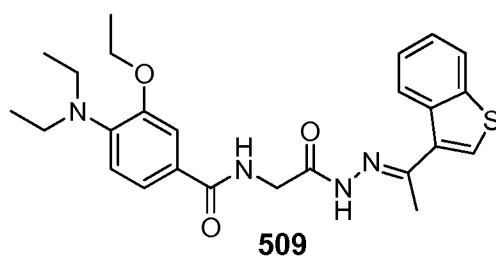
[0564] Compound **506** was obtained following the procedure for obtaining compound **500** using 3,4-dinitrobenzoic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **506** was obtained as a white solid (25 mg, 30.9%). +ESI-MS:m/z 494.2 [M+H]⁺.



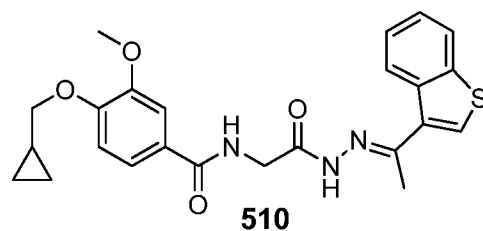
[0565] Compound **507** was obtained following the procedure for obtaining compound **500** using 3,4-dinitrobenzoic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **507** was obtained as a white solid (30 mg, yield: 30.0%). +ESI-MS:m/z 469.94 [M+H]⁺.



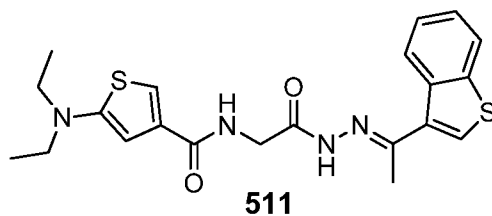
[0566] Compound **508** was obtained following the procedure for obtaining compound **500** modifying the alkylation step as appropriate. Compound **508** was obtained as a white solid (20 mg, 43%). ESI-LCMS: m/z 425 [M+H]⁺.



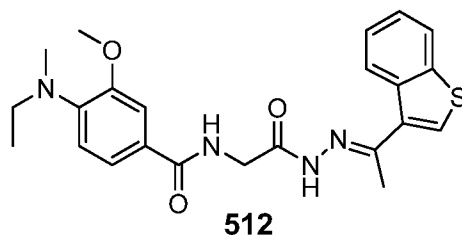
[0567] Compound **509** was obtained following the procedure for obtaining compound **500** using 3-hydroxy-4-nitrobenzoic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **509** was obtained as a white solid (50 mg, 37.9%). +ESI-MS:m/z 467.0 [M+H]⁺.



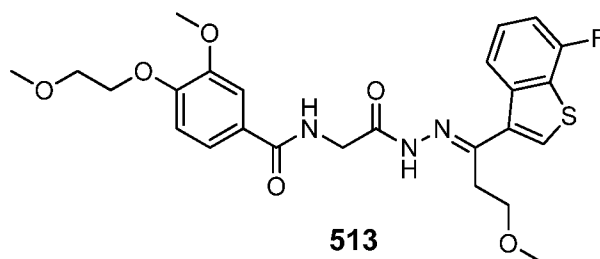
[0568] Compound **510** was obtained following the procedure for obtaining compound **500** starting from intermediate 3 using 4-hydroxy-3-methoxybenzoic acid in place of ethyl 4-amino-3-methoxybenzoate. Compound **510** was obtained as a white solid (60 mg, yield: 26%). +ESI-MS:m/z 452.1 [M+H]⁺.



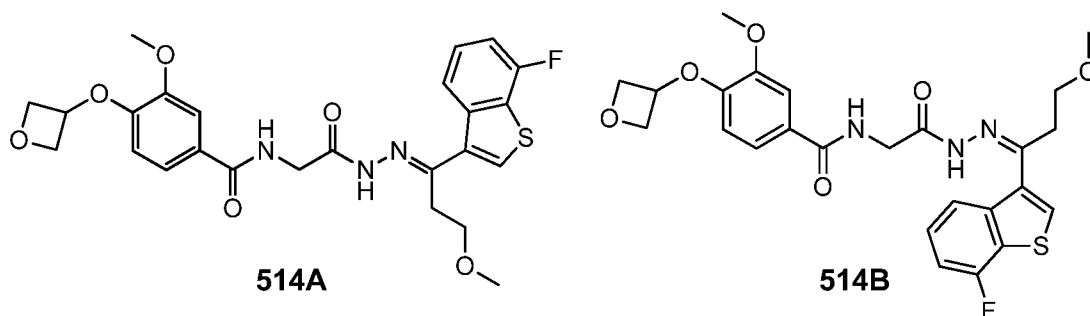
[0569] Compound **511** was obtained following the procedure for obtaining compound **500** using 5-nitrothiophene-3-carboxylic acid in place of 3-methoxy-4-nitrobenzoic acid. Compound **511** was obtained as a white solid (30 mg, 19%). +ESI-MS:m/z 429.0 [M+H]⁺.



[0570] Compound **512** was obtained following the procedure for obtaining compound **500** modifying the alkylation step as appropriate. Compound **512** was obtained as a white solid (78 mg, 50.0%). +ESI-MS:m/z 439.0 [M+H]⁺.

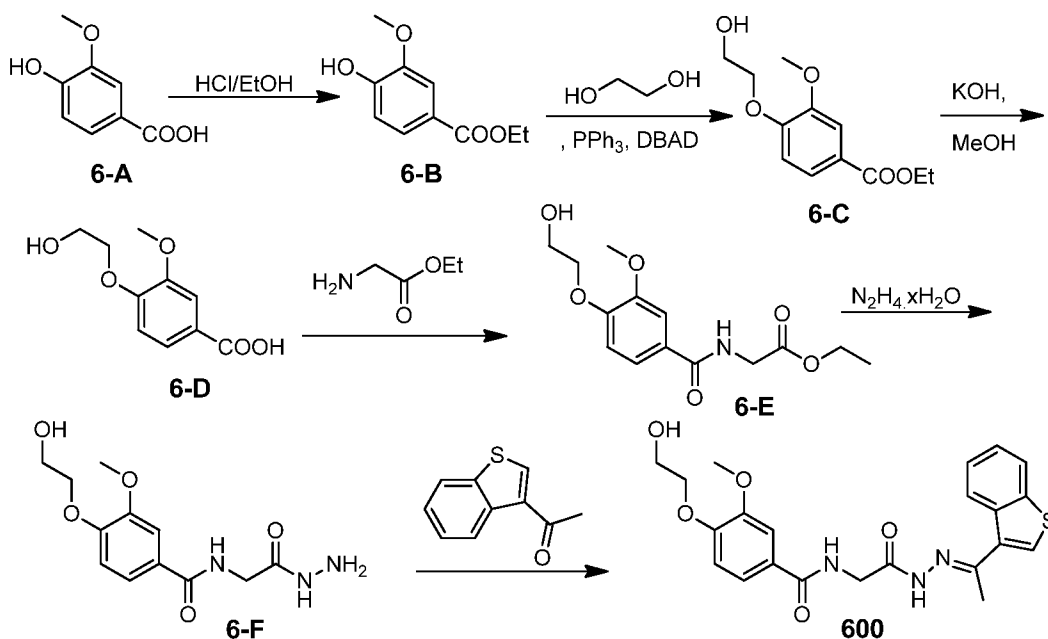


[0571] Compound **513** was obtained following the procedure for obtaining compound **500**. Compound **513** was obtained as a white solid (128 mg, 57%). +ESI-MS:m/z 518.1 [M+H]⁺.



[0572] Compound **514A** and compound **514B** were obtained following the procedure for obtaining compound **500** using 4-hydroxy-3-methoxy-benzoic acid ethyl ester in place of ethyl 4-amino-3-methoxybenzoate. Compound **514A** (35 mg, 13.9%) and compound **514B** (15 mg, 6.0%) were obtained as a white solid. Compound **514A**: +ESI-MS:m/z 516.4 [M+H]⁺. Compound **514B**: +ESI-MS:m/z 516.2 [M+H]⁺.

EXAMPLE 6
Preparation of Compound 600



[0573] To a solution of 4-hydroxy-3-methoxybenzoic acid (**6-A**) (5 g, 29.7 mmol) in EtOH (20 mL) was added HCl. The mixture was stirred for 60°C for 14 h. The reaction was concentrated to afford crude ethyl 4-hydroxy-3-methoxybenzoate (**6-B**) (4.6 g, 79% yield).

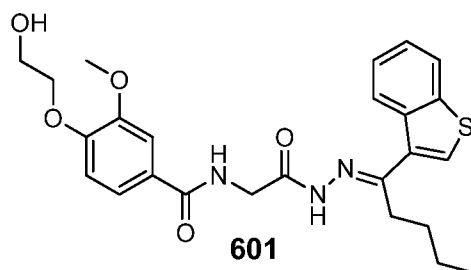
[0574] To a solution of ethyl 4-hydroxy-3-methoxybenzoate (**6-B**) (2.3 g, 11.7 mmol) and ethylene glycol (738 mg, 11.89 mmol) in anhydrous THF (20 mL) was added triphenylphosphine (6240 mg, 23.78 mmol) under N₂. The mixture was cooled to 0°C, DEAD (3.9 g, 24 mmol) was added in portions. The solution was stirred at rt for 2 h. The crude product was purified by column chromatography on silica gel eluted with PE:EA = 20:1 to afford ethyl 4-(2-hydroxyethoxy)-3-methoxybenzoate (**6-C**) (1500 mg, 53.2%).

[0575] To a solution of ethyl 4-(2-hydroxyethoxy)-3-methoxybenzoate (**6-C**) (1 g, 4.2 mmol) in MeOH (20 mL) was added KOH (1.5 g, 22.7 mmol). The mixture was stirred at 40°C for 2 h. Solvent was removed and the mixture was dissolved in water. The aqueous mixture was washed three times with tert-butylmethylether and the aqueous phase was maintained. The aqueous phase was treated with HCl to attain pH = 6. The precipitate was collected by filtration. The residue was washed by water to afford 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (**6-D**) (780 mg, 88%).

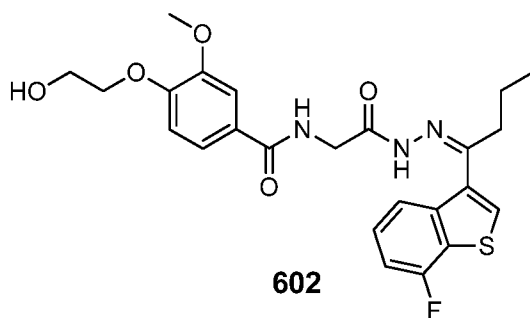
[0576] To a solution of 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (**6-D**) (300 mg, 1.41 mmol) in DCM (10 mL) was added HATU (1075 mg, 2.82 mmol) and DIPEA (456 mg, 3.53 mmol), the mixture was stirred at rt for 30 mins, then was treated with glycine ethyl ester (197 mg, 1.41 mmol). The mixture was stirred at rt for another 15 h. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **6-E** as a white solid (385 mg, 91.9%).

[0577] To a solution of **6-E** (297 mg, 1 mmol) in anhydrous ethanol (10 mL) was added $\text{N}_2\text{H}_4 \cdot x\text{H}_2\text{O}$ (481 mg, 15 mmol), the mixture was stirred at 80°C for 15 h. Then the mixture was allowed to cool to rt and a white precipitate was formed. The precipitate was filtered and washed with EtOH (20 mL) to afford **6-F** as a white product (198 mg, 70%).

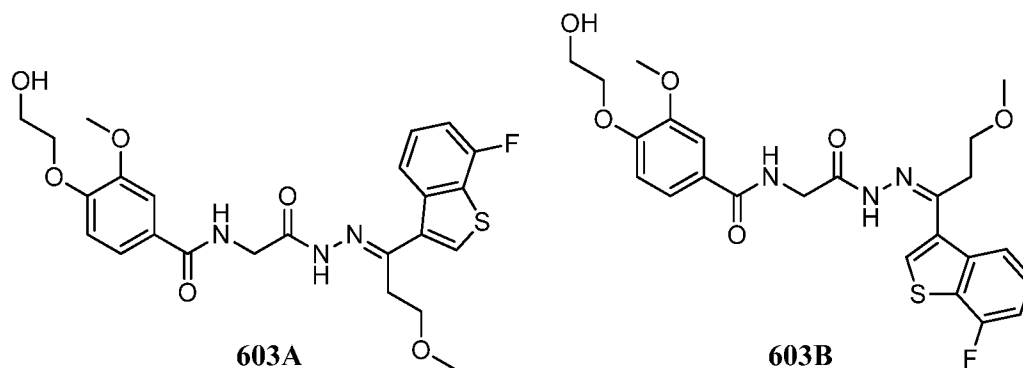
[0578] Compound **6-F** (100 mg, 0.35 mmol) was dissolved in anhydrous EtOH (5 mL). To this solution was added 1-benzo[*b*]thiophene-3-yl-ethanone (62 mg, 0.353 mmol) and AcOH (0.4 mL). The mixture was stirred at 60°C for 10 h. The mixture was filtered, and the solid was washed with EtOH (10 mL) and EA (10 mL) to afford compound **600** (85 mg, 55%). +ESI-MS:*m/z* 442.0.



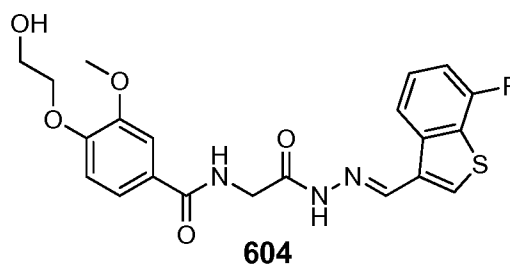
[0579] Compound **601** was obtained following the procedure for obtaining compound **600** using 1-(7-fluorobenzo[*b*]thiophen-3-yl)pentan-1-one in place of 1-benzo[*b*]thiophene-3-yl-ethanone. Compound **601** was obtained as a white solid (30 mg, yield: 28.6%). +ESI-MS:*m/z* 485.92 [$\text{M}+\text{H}$]⁺.



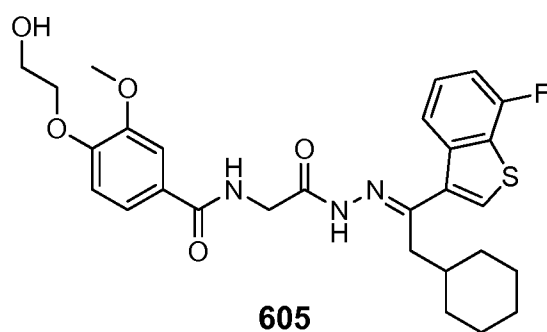
[0580] Compound **602** was obtained following the procedure for obtaining compound **600** using 1-(7-fluorobenzo[*b*]thiophen-3-yl)pentan-1-one in place of 1-benzo[*b*]thiophene-3-yl-ethanone. Compound **602** was obtained as a white solid (45 mg, 10.9%). +ESI-MS:*m/z* 501.9 [M+H]⁺.



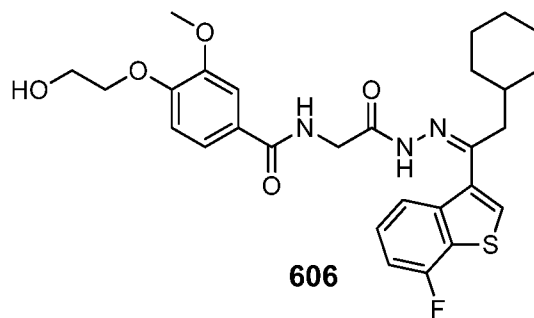
[0581] Compound **603A** and compound **603B** were obtained following the procedure for obtaining compound **600** using 1-(7-fluorobenzo[*b*]thiophen-3-yl)-3-methoxypropan-1-one in place of 1-benzo[*b*]thiophene-3-yl-ethanone. Compound **603A** was obtained as a white solid (200 mg, yield: 47.0%) and compound **603B** was obtained as a white solid (50 mg, yield: 11.5%). Compound **603A**: +ESI-MS:*m/z* 503.82 [M+H]⁺. Compound **603B**: +ESI-MS:*m/z* 503.87 [M+H]⁺.



[0582] Compound **604** was obtained following the procedure for obtaining compound **600** using 7-fluorobenzo[*b*]thiophene-3-carboxaldehyde in place of 1-benzo[*b*]thiophene-3-yl-ethanone. Compound **604** was obtained as a white solid (40 mg, yield: 85.1%). +ESI-MS:*m/z* 446.0 [M+H]⁺.

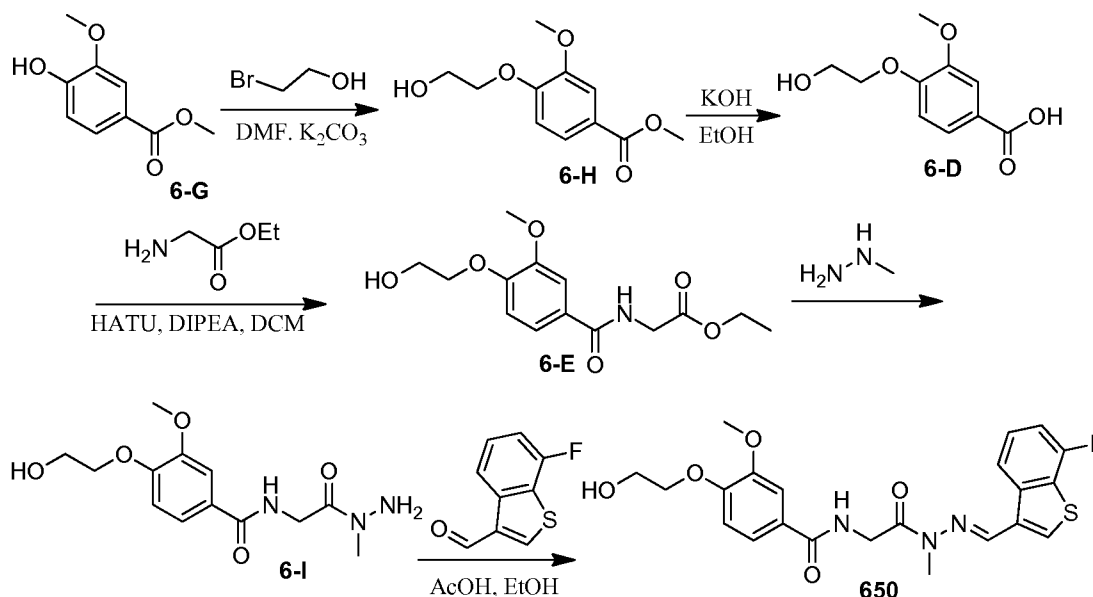


[0583] Compound **605** was obtained following the procedure for obtaining compound **600** using 2-cyclohexyl-1-(7-fluorobenzo[*b*]thiophen-3-yl)ethanone in place of 1-benzo[*b*]thiophene-3-yl-ethanone. Compound **605** was obtained as a white solid (80 mg, 20.5%). +ESI-MS:*m/z* 542.1 [M+H]⁺.



[0584] Compound **606** was obtained following the procedure for obtaining compound **600** using 2-cyclohexyl-1-(7-fluorobenzo[*b*]thiophen-3-yl)ethanone in place of 1-benzo[*b*]thiophene-3-yl-ethanone. Compound **606** was obtained as a white solid (40 mg, 10.2%). +ESI-MS:*m/z* 542.7 [M+H]⁺.

EXAMPLE 6-1
Preparation of Compound 650



[0585] To a solution of methyl 4-hydroxy-3-methoxybenzoate (**6-G**) (15 g, 83 mmol) and K_2CO_3 (34 g, 246 mmol) in DMF (100 mL) was added 2-bromoethanol (30 g, 241 mmol) at 25°C. The mixture was stirred for 15 h at 90 °C. The mixture was poured into water and extracted with EA, the combined organic phase was dried over anhydrous Na_2SO_4 , filtered and the solvent was removed to provide a residue. The residue was purified by chromatography on silica gel (PE:EA = 1:1) to afford methyl 4-(2-hydroxyethoxy)-3-methoxybenzoate (**6-H**) (9.5 g, 60 %).

[0586] To a solution of methyl 4-(2-hydroxyethoxy)-3-methoxybenzoate (**6-H**) (9.0 g, 42 mmol) in EtOH (50 mL) was added KOH (15 g, 268 mmol) in H_2O (50 mL). The mixture was stirred for 2 h at 70°C. The mixture was concentrated and a precipitate was formed by addition of 2 N HCl. The precipitate was collected by filtration and washed with H_2O to afford 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (**6-D**) (6.0 g, 60 %). ^1H NMR (400 MHz, $DMSO-d_6$) δ 12.63 (br, 1H), 7.55-7.52 (dd, J = 2.0 , 8.4 Hz, 1H), 7.44 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 4.89 (br, 1H), 4.06-4.03 (m, 2H), 3.80 (s, 3H), 3.75-3.73 (m, 2H).

[0587] To a solution of 4-(2-hydroxyethoxy)-3-methoxybenzoic acid (**6-D**) (6.0 g, 28 mmol), HATU (15 g, 39 mmol) and DIPEA (9 g, 70 mmol) in anhydrous DCM (100 mL) was added ethyl 2-aminoacetate (3.9 g, 28 mmol) at 25°C. The mixture was stirred for 10 h and then diluted with 1.0 N aqueous $NaHCO_3$ solution, extracted with EA. The

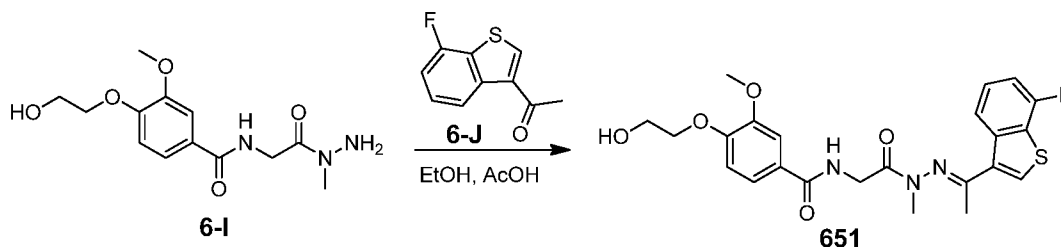
combined organic phase was dried over anhydrous Na_2SO_4 , and concentrated to afford a residue. The residue was purified by column chromatography to afford **6-E** (4.0 g, 45 %). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.78-8.75 (br, 1H), 7.45 (m, 1H), 7.43 (s, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 4.87-4.84 (m, 1H), 4.11-4.06 (m, 2H), 4.02-3.95 (m, 4H), 3.78 (s, 3H), 3.72-3.69 (m, 2H), 1.19-1.15 (m, 3H).

[0588] To a solution of **6-E** (2.5 g, 8.4 mmol) in anhydrous EtOH (15 mL) was added methylhydrazine (18.3 g, 39 mmol). The mixture was stirred for 10 h at 70°C and then cooled to rt. The solvent was removed to afford a residue and the residue was purified by prep-HPLC to afford **6-I** (300 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.26 (br, 1H), 7.47 (m, 1H), 7.45 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.23 (m, 2H), 4.04-4.01 (m, 2H), 3.80 (s, 3H), 3.74-3.72 (m, 2H), 3.12 (m, 3H).

[0589] To a solution of **6-I** (200 mg, 0.63 mmol) in anhydrous EtOH (6 mL) and AcOH (0.6 mL) was added 7-fluorobenzo[*b*]thiophene-3-carbaldehyde (121 mg, 0.63 mmol). The mixture was stirred at 70°C for 10 h and then cooled to rt. A precipitate was formed and was collected by filtration. The solid was washed with EA and EtOH to afford compound **650** (120 mg, 30 %). ESI-LCMS: *m/z* 459.9 [M+H]⁺.

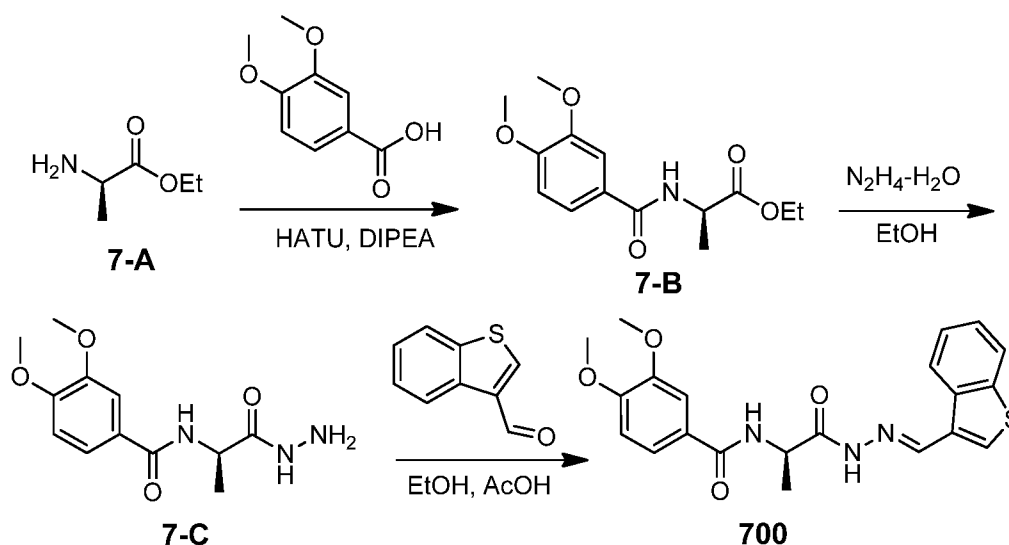
EXAMPLE 6-2

Preparation of Compound 651



[0590] To a solution of **6-I** (297 mg, 1 mmol) in anhydrous EtOH (6 mL) and AcOH (0.6 mL) was added 1-(7-fluorobenzo[*b*]thiophen-3-yl)ethanone (**6-J**) (250 mg, 1.29 mmol). The solution was stirred at 70°C for 10 h and then cooled to rt. The solution was concentrated and the residue was purified by prep-HPLC to afford compound **651** (60 mg, 20 %). ESI-LCMS: *m/z* 474 [M+H]⁺.

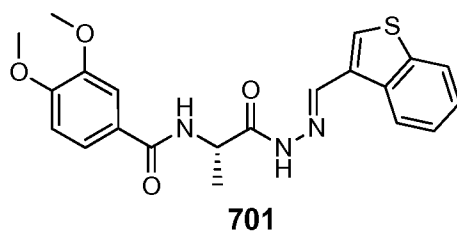
EXAMPLE 7
Preparation of Compound 700



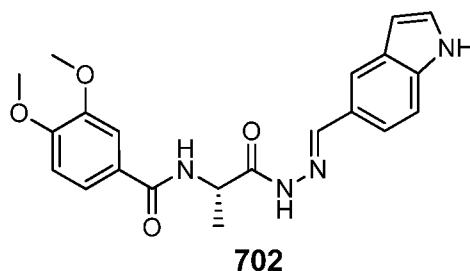
[0591] To a solution of 3,4-dimethoxybenzoic acid (3.0 g, 14.3 mmol), HATU (6.5 g, 17.1 mmol) and DIPEA (3.1 g, 24 mmol) in anhydrous DCM (30 mL) was added D-Alanine ethyl ester (**7-A**) (2.5 g, 16.5 mmol) at 25°C. The mixture was stirred for 10 h and then diluted with 1.0 N aqueous NaHCO₃ solution (50 mL × 2), extracted with EA (50 mL × 2). The combined organic phase dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford **7-B** (2.5 g, 40%) used for next step directly without purification

[0592] To a solution of **7-B** (2.5 g, 8.9 mol) in anhydrous EtOH (50 mL) was added NH₂NH₂·H₂O (2.9 g, 90 mmol). The mixture was stirred for 10 h at 70°C and then cooled to rt, A precipitate was formed and was collected by filtration to afford **7-C** (1.8 g, 60 %) used in the next step without purification.

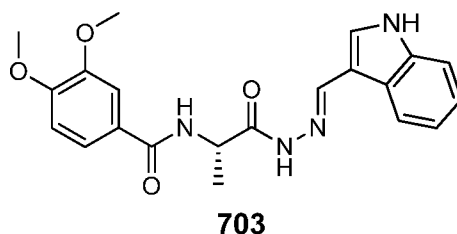
[0593] To a solution of **7-C** (250 mg, 0.94 mmol) in anhydrous EtOH (6 mL) and AcOH (0.2 mL) was added benzo[*b*]thiophene-3-carboxaldehyde (151 mg, 0.94 mmol). The solution was stirred at 70°C for 10 h and then cooled to rt. A precipitate was formed and was collected by filtration. The solid was washed with EA and EtOH to afford compound **700** (50 mg, 10 %). ESI-LCMS: *m/z* 412 [M+H]⁺.



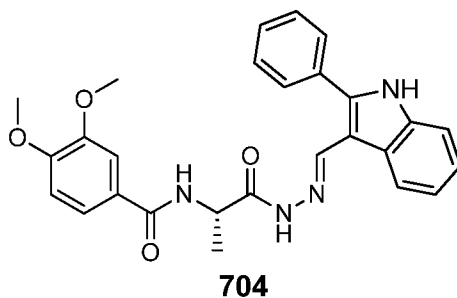
[0594] Compound **701** was obtained following the procedure for obtaining compound **700** using L-Alanine ethyl ester in place of D-Alanine ethyl ester. Compound **701** was obtained as a white solid (133 mg, 77.8%). +ESI-MS:m/z 368.0 [M+H]⁺.



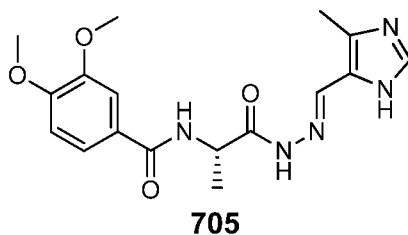
[0595] Compound **702** was obtained following the procedure for obtaining compound **700** using L-Alanine ethyl ester in place of D-Alanine ethyl ester and using 1H-indole-5-carboxaldehyde in place of benzo[b]thiophene-3-carboxaldehyde. Compound **702** was obtained as a white solid (120 mg, 71.8%). +ESI-MS:m/z 395.0 [M+H]⁺.



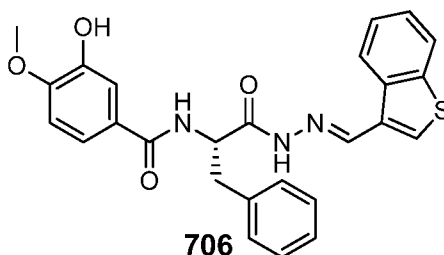
[0596] Compound **703** was obtained following the procedure for obtaining compound **700** using L-Alanine ethyl ester in place of D-Alanine ethyl ester and using 1H-indole-3-carboxaldehyde in place of benzo[b]thiophene-3-carboxaldehyde. Compound **703** was obtained as a white solid (134 mg, 78.8%). +ESI-MS:m/z 395.0 [M+H]⁺.



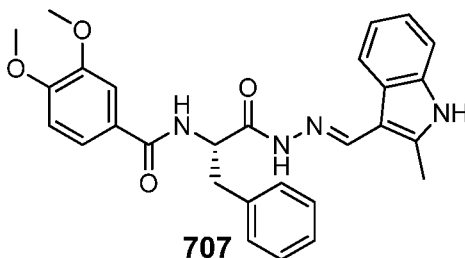
[0597] Compound **704** was obtained following the procedure for obtaining compound **700** using L-Alanine ethyl ester in place of D-Alanine ethyl ester and using 2-phenyl-1*H*-indole-3-carboxaldehyde in place of benzo[*b*]thiophene-3-carboxaldehyde. Compound **704** was obtained as a white solid (135 mg, 79.2%). +ESI-MS:*m/z* 471.0 [M+H]⁺.



[0598] Compound **705** was obtained following the procedure for obtaining compound **700** using L-Alanine ethyl ester in place of D-Alanine ethyl ester and using 4-methyl-1*H*-imidazole-5-carboxaldehyde in place of benzo[*b*]thiophene-3-carboxaldehyde. Compound **705** was obtained as a white solid (131 mg, 76.6%). +ESI-MS:*m/z* 360.0 [M+H]⁺.

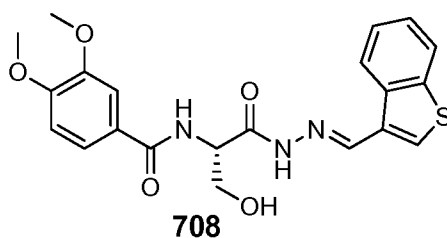


[0599] Compound **706** was obtained following the procedure for obtaining compound **700** using 3-hydroxy-4-methoxybenzoic acid in place of 3,4-dimethoxybenzoic acid and using L-Phenylalanine ethyl ester in place of D-Alanine ethyl ester. Compound **706** was obtained as a white solid (32 mg, 24.4%). +ESI-MS:*m/z* 438.1 [M+H]⁺.

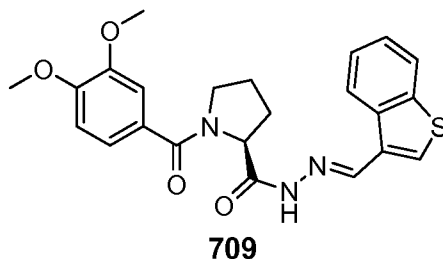


[0600] Compound **707** was obtained following the procedure for obtaining compound **700** using L-Phenylalanine ethyl ester in place of D-Alanine ethyl ester and 2-

methyl-1*H*-indole-3-carboxaldehyde in place of benzo[*b*]thiophene-3-carboxaldehyde. Compound **707** was obtained as a white solid (30 mg, 24.7%). +ESI-MS: m/z 485.2 $[M+H]^+$.

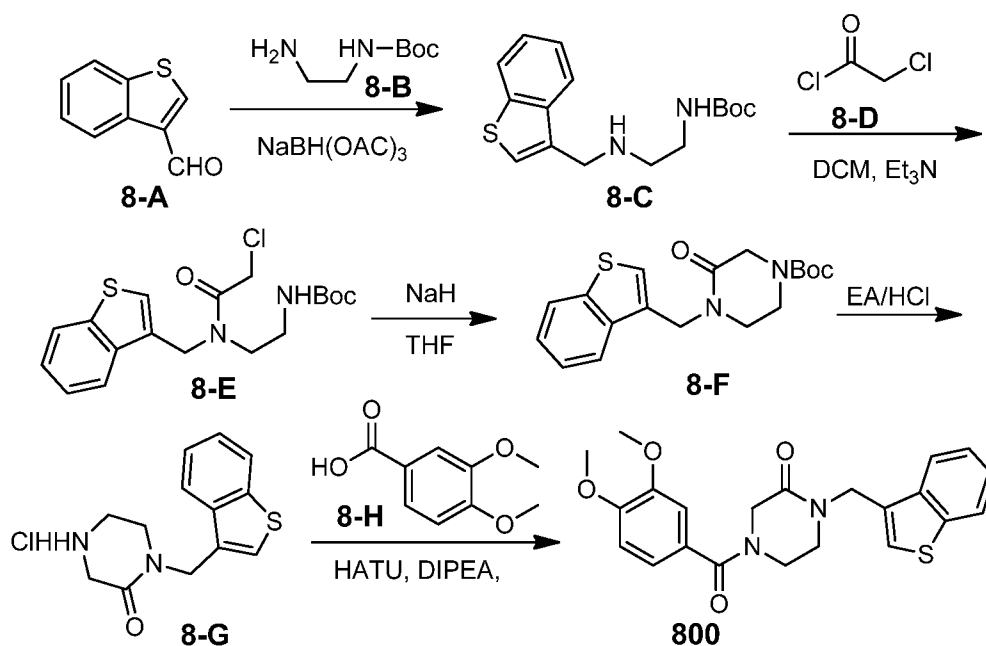


[0601] Compound **708** was obtained essentially following the procedure for obtaining compound **700**. Compound **708** was obtained as a white solid (3 mg, 7.05%). +ESI-MS: m/z 428.0 $[M+H]^+$.



[0602] Compound **709** was obtained essentially following the procedure for obtaining compound **700**. Compound **709** was obtained as a white solid (13 mg, 22.7%). +ESI-MS: m/z 438.1 $[M+H]^+$.

EXAMPLE 8 **Preparation of Compound 800**



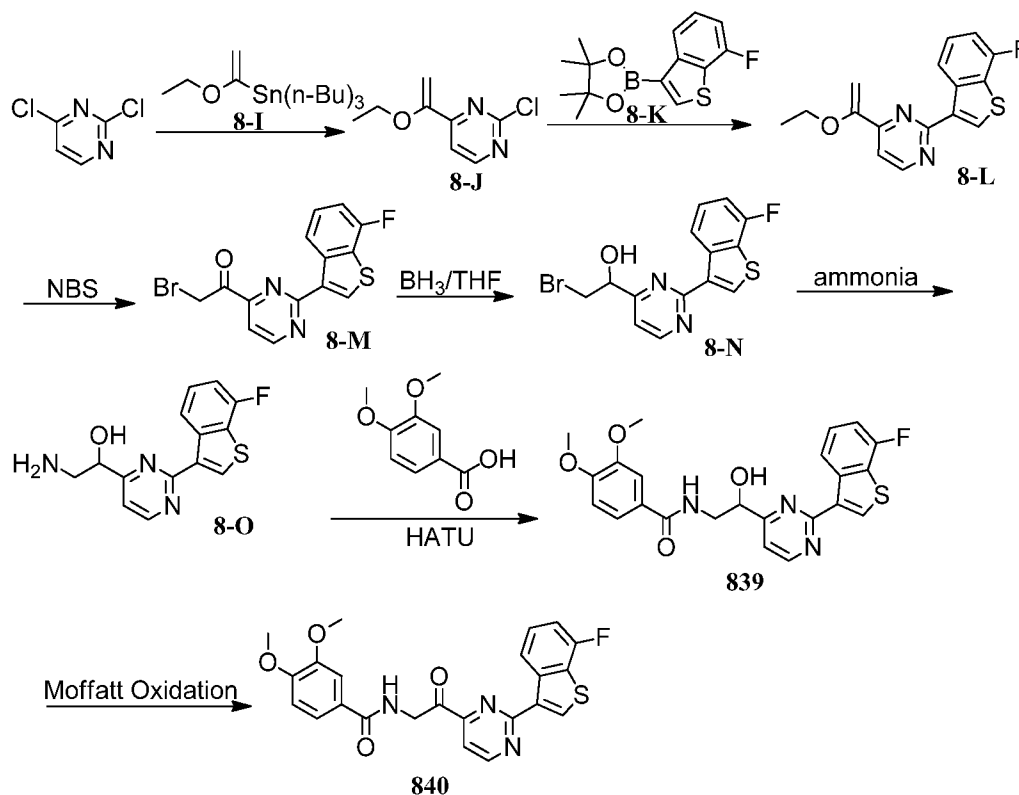
[0603] To a solution of benzo[*b*]thiophene-3-carboxaldehyde (**8-a**) (10 g, 62 mmol) in THF (100 mL), N-Boc-ethylenediamine (**8-B**) was added. The mixture was stirred for 1 hour at rt. Then NaBH(OAc)₃ was added. The solution was stirred for 15 h at rt. The mixture was treated with aqueous NaHCO₃ and extracted with EA. The organic phase was concentrated and the residue was purified by chromatography on silica gel (PE:EA = 10:1-5:1) to afford **8-C** (7 g, yield: 37.4%).

[0604] To a solution of **8-C** (0.4 g, 1.3 mmol) in DCM (5 mL), was added Et₃N (0.132g, 1.3 mmol). Then chloroacetyl chloride (**8-D**) (0.15 g, 1.3 mmol) was added dropwise at 0°C. The solution was stirred for 1 hour and then treated with aqueous NH₄Cl followed by extraction with DCM. The organic phase was removed to afford **8-E** as a residue. The residue was dissolved in THF and then NaH was added slowly at 0°C. The solution was stirred for 2 h and then treated with aqueous NH₄Cl followed by extraction with DCM. The organic phase was removed to afford crude **8-F** (0.3 g, yield: 65.0%)

[0605] To a solution of **8-F** (0.3 g, 0.86 mmol) in ethylacetate (5 mL), a solution of HCl in ethylacetate was added. The mixture was stirred for 4 h at rt. The precipitate was collected and washed with EA (EA) to afford crude **8-G** (0.18 g, 84.9%)

[0606] To a solution of **8-G** (90 mg, 0.316 mmol) in DCM (3 mL), 3,4-dimethoxybenzoic acid (**8-H**) (58mg, 0.316 mmol), HATU (180 mg, 0.47 mmol) and DIPEA (122 mg, 0.95 mmol) were added. The mixture was stirred for 3 h at rt. The mixture was washed with water and partitioned. The organic phase was dried over Na₂SO₄. Then the solvent was removed and the residue was purified by recrystallization to afford compound **800** (60 mg, 46.0 %). +ESI-MS:m/z 411.1 [M+H]⁺.

EXAMPLE 8-1
Preparation of Compounds 839 and 840



[0607] To a stirred solution of 2,4-dichloropyrimidine (10 g, 1.0eq), KF (12.9 g, 4.0 eq), Pd(dppf)Cl₂ (0.5 g) in dry 100 mL of DMF was added tributyl(1-ethoxyvinyl)stannane (**8-I**) (25.4 g, 1.05 eq), and the mixture was stirred at 85°C under N₂ over 4 h. The mixture was cooled to rt, poured into ice-cold water and extracted by MTBE, The combined organic layer was washed with water and brine, concentrated, purified by silica gel (PE/EA: 100/1 to 50/1) to afford 2-chloro-4-(1-ethoxyvinyl)pyrimidine (**8-J**) (10 g, 80% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.61-8.60 (s, 1H), 7.57-7.56 (s, 1H), 5.73-5.72 (s, 1H), 4.58-4.57 (s, 1H), 4.00-3.94 (q, 2H), 1.45-1.42 (t, 3H).

[0608] To a stirred solution of 2-chloro-4-(1-ethoxyvinyl)pyrimidine (**8-J**) (2 g, 1.0 eq), KF (2.5 g, 4.0 eq), Pd(dppf)Cl₂ (0.2 g) in 20 mL of dry DMF was added 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**8-K**) (3.3 g, 1.1 eq), and the mixture was stirred at 85°C under N₂ over 4 h. The mixture was cooled to rt, poured into ice-cold water and extracted by MTBE. The combined organic extract was washed with water and brine, concentrated, purified by silica gel (PE/EA: 100/1 to 50/1) to afford 2.2 g of

4-(1-ethoxyvinyl)-2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidine (**8-L**) (67% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.93-8.90 (d, 1H), 8.84-8.83 (d, 1H), 8.64-8.63 (s, 1H), 7.55-7.54 (d, 1H), 7.47-7.46 (t, 1H), 7.15-7.08 (m, 1H), 5.84-5.83 (d, 1H), 4.59-4.58 (d, 1H), 4.03-3.98 (t, 2H), 1.48-1.41 (q, 3H).

[0609] To a stirred solution of 4-(1-ethoxyvinyl)-2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidine (**8-L**) (1.2 g, 1.0 eq) in 8 mL of THF and 3 mL of water was added NBS (0.75 g, 1.05 eq) at 0°C portionwise, after this addition, the mixture was stirred at 0°C for 10 mins, then quenched by saturated NaHCO₃, and extracted with EA. The combined organic extracted was purified by silica gel to afford 1.0 g of 2-bromo-1-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)ethanone (**8-M**) (70% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.12-9.11 (d, 1H), 8.88-8.87 (d, 1H), 8.74-8.73 (s, 1H), 7.84-7.83 (d, 1H), 7.54-7.48 (m, 1H), 7.18-7.13 (m, 1H), 4.88 (s, 1H).

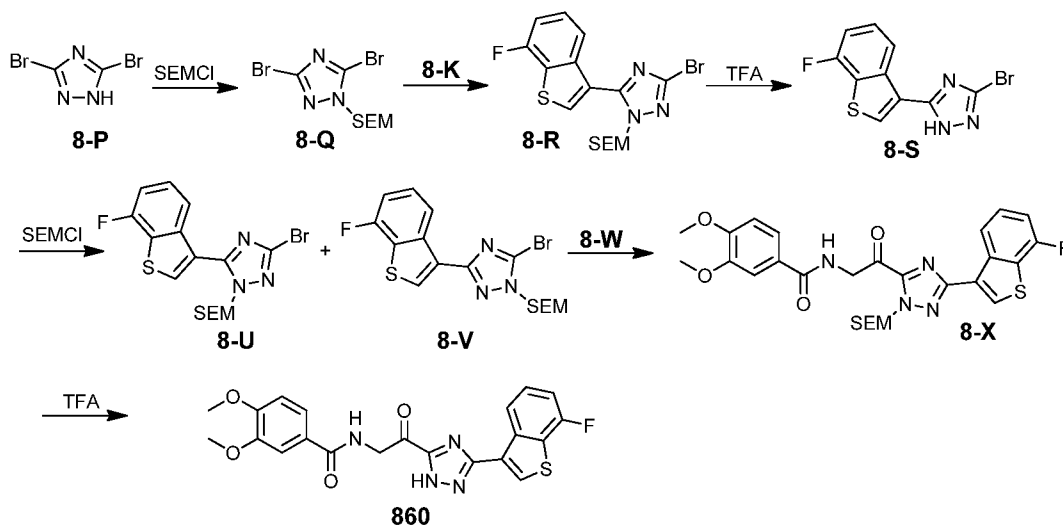
[0610] A mixture of 2-bromo-1-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)ethanone (**8-M**) (1 g, 1.0 eq) in dry THF at -20°C under N₂ was added dropwise 1.0M BH₃/THF (2.85 mL, 1.0 eq), after this addition, the mixture was stirred at -20°C for 30 mins and allowed to warm to 0°C for 1 hour. The reaction was quenched with MeOH, washed with NaHCO₃, and brine, dried over Na₂SO₄, concentrated to afford crude 2-bromo-1-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)ethanol (**8-N**) (1 g, 100%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.88-8.87 (d, 1H), 8.82-8.79 (d, 1H), 8.65-8.64 (s, 1H), 7.50-7.45 (m, 1H), 7.42-7.40 (d, 1H), 7.16-7.11 (m, 1H), 5.08-5.04 (br, 1H), 4.15-4.10 (q, 1H), 3.97-3.93 (q, 1H), 3.68-3.66 (br, 1H).

[0611] A mixture of 2-bromo-1-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)ethanone (**8-N**) (0.4 g, 1.0 eq) in 8 mL of EtOH and 8 mL of aqueous ammonia in a seal tube was heated to 100°C for 5 h. The mixture was concentrated to afford a residue. The residue was dissolved in EA, washed with saturated NaHCO₃, and brine, dried over Na₂SO₄, concentrated to afford crude 2-amino-1-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)ethanol (**8-O**) (0.3 g, 92%) as a pale yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98-8.71 (m, 3H), 7.60-7.50 (m, 2H), 7.37-7.33 (br, 1H), 5.78-5.72 (s, 1H), 4.63-4.58 (br, 1H), 3.07-3.01 (m, 1H), 2.82-2.75 (m, 1H).

[0612] A mixture of 3,4-dimethoxybenzoic acid (0.189 g, 1.2 eq) and HATU (0.427 g, 1.3 eq), DIPEA (0.199 g, 2.0 eq) in DMF was stirred at rt for 10 mins, then 2-amino-1-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)ethanol (**8-O**) (0.25 g, 1.0 eq.) was added. The mixture was stirred at rt for an additional 2 h, then treated with NaHCO₃, washed with brine, concentrated, purified by silica gel to afford N-(2-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)-2-hydroxyethyl)-3,4-dimethoxy-benzamide (compound **839**) (0.25 g, 51%) as a white solid. ESI-LCMS: m/z 454.1 [M+H]⁺.

[0613] A stirred solution of anhydrous pyridine (12.5 mg, 1.2 eq) in anhydrous DMSO (0.2 mL) cooled with a cold water bath (10 °C) under argon was treated with TFA (9 mg, 0.6 eq). After addition, the TFA/pyridine solution was warmed to rt and added (with syringe) very slowly to a stirred solution of N-(2-(2-(7-fluorobenzo[b]thiophen-3-yl)pyrimidin-4-yl)-2-hydroxyethyl)-3,4-dimethoxy-benzamide (**839**) (60 mg, 1.0 eq) and DCC (81.8 mg, 3.0 eq) in anhydrous DMSO (0.5 mL) cooled with cold water (~10°C) under argon. The mixture was stirred at rt (22-24 °C) under argon for 18 h and then cooled with cold water (~10°C). The cooled reaction was quenched slowly with water (1 mL) and stirred at rt for 1 hour. The isolated crude product was purified by prep-HPLC to afford compound **840** (6 mg, 9.9%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.28-9.26 (d, 1H), 8.08 (s, 1H), 8.95-8.93 (d, 1H), 8.87-8.86 (t, 1H), 7.88-7.86 (d, 1H), 7.68-7.60 (m, 1H), 7.57-7.52 (d, 1H), 7.51-7.50 (s, 1H), 7.42-7.37 (t, 1H), 7.08-7.04 (d, 1H), 5.07-5.05 (d, 1H), 3.83-3.81 (d, 6H).

EXAMPLE 8-2
Preparation of Compound 860



[0614] A mixture of 3,5-dibromo-1H-1,2,4-triazole (**8-P**) (11 g, 50 mmol) and Et₃N (10 mL) in DCM (200 mL) at rt was added 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) (8.5 g, 50 mmol) in portions. Subsequently, the mixture was stirred for 30 mins at rt, then the volatiles were removed. Purification by column chromatography on silica gel (PE) afforded **8-Q** as colorless oil (17 g, 96%). +ESI-MS: m/z 299.7 [M-57]⁺.

[0615] A flask with a magnetic stirring bar under a N₂ atmosphere was charged with **8-Q** (1.05 g, 3 mmol), **8-K** (920 mg, 3.4 mmol), Pd(dppf)Cl₂ (24 mg, 1 mol%), Cs₂CO₃ (3 g, 3 eq), and dry DMF (50 mL). The mixture was stirred for 10 h at 100 °C, then 50 mL water and 50 mL EA were added. The organic layer was separated and maintained, and the aqueous phase extracted with EA. The combined organic phases were dried (MgSO₄) and the volatiles were removed. Purification by column chromatography on silica gel (PE) afforded **8-R** as an oil (800 mg, 62%). +ESI-MS: m/z 429.7 [M+H]⁺.

[0616] Compound **8-R** (400 mg, 0.93 mmol) in DCM (10 mL) was treated with TFA (10 mL). The mixture was stirred for 2 h at rt, then the solvent was evaporated to afford the crude product as an oil. The crude product was purified by column chromatography on silica gel (EA) to afford **8-S**. (277 mg, 100%). +ESI-MS: m/z 297.7 [M+H]⁺.

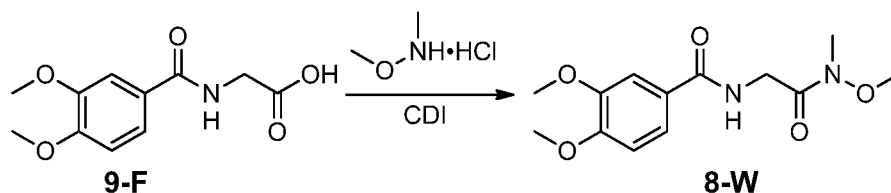
[0617] To a mixture of **8-S** (277 mg, 0.93 mmol) and Et₃N (1 mL) in DCM (50 mL) at rt was added SEMCl (166 mg, 1 mmol) in portions, after that, the mixture was stirred for additional 30 mins at rt, then the volatiles were removed under reduced pressure.

Purification by column chromatography on silica gel (PE) provided **8-U** and **8-V** as colorless oil (328 mg, 100%).

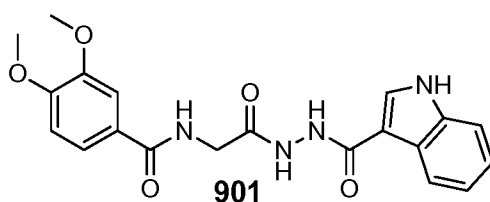
[0618] A mixture of **8-U** and **8-V** (328 mg, 0.93 mmol) and **8-W** (282 mg, 1 mmol) in THF (10 mL) at rt under nitrogen atmosphere was treated with *i*-PrMgCl (0.2 mL, 1.3 M) in portions, after that, the mixture was stirred for additional 10 mins at rt, quenched with NH₄Cl saturated solution, extracted with EA, dried over Na₂SO₄, then the volatiles were removed. Purification by column chromatography on silica gel (PE/EA = 2/1) afforded **8-X** as colorless oil (200 mg, 36 %). +ESI-MS: *m/z* 571.1 [M+H]⁺

[0619] To **8-X** (200 mg, 0.38 mmol) in DCM (10 mL) was added TFA (10 mL). The mixture was stirred for 2 h at rt, and then the solvent was removed to afford the crude product as oil. The crude product was purified by Pre-HPLC to afford the compound **860** (50 mg, 100%). +ESI-MS: *m/z* 440.8 [M+H]⁺.

EXAMPLE 8-3 Preparation of Compound 8-W

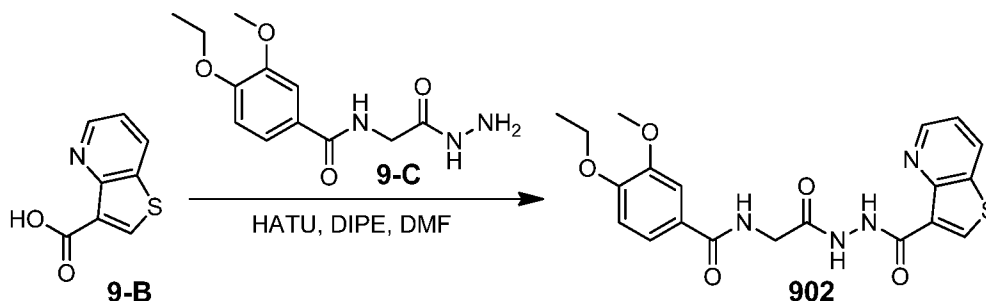


[0620] To a solution of 2-(3,4-dimethoxybenzamido)acetic acid (**9-F**) (4.8 g, 20 mmol) in DCM at rt was added CDI (3.2 g, 20 mmol) in portions, the mixture was stirred for 30 mins at rt, and then N,O-dimethylhydroxylamine hydrochloride was added, and stirring was continued for 4 h. After 4 h, 100 mL water was added to the stirring mixture and the layers were separated. The organic layer was maintained and the aqueous phase extracted with CH₂Cl₂. The combined organic phases were dried (MgSO₄) and the volatiles were removed to afford a residue. Purification by column chromatography on silica gel (EA/PE = 1:1) afforded **8-W** as a white solid (5.6, 100%). +ESI-MS: *m/z* 304.8 [M+Na]⁺.



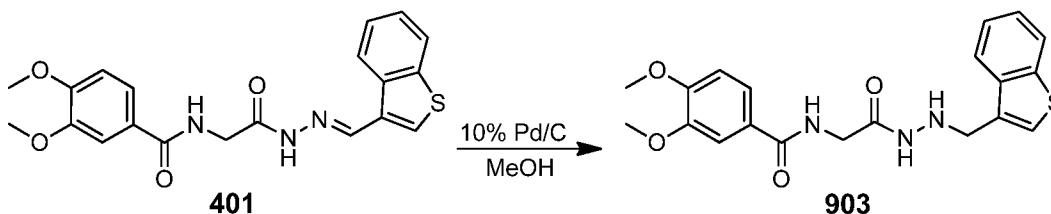
[0623] Compound **901** was obtained following the procedure for obtaining compound **900** using 1*H*-indole-3-carboxylic acid in place of benzo[*b*]thiophene-3-carboxylic acid. Compound **901** was obtained as a white solid (10 mg, 34.8%). +ESI-MS:*m/z* 396.0 [*M*+*H*]⁺.

EXAMPLE 9-1 **Preparation of Compound 902**



[0624] To a solution of thieno[3,2-*b*]pyridine-3-carboxylic acid (**9-B**) (50 mg, 0.277 mmol) in DMF (2 mL), **9-C** (100 mg, 0.374 mmol), HATU (275 mg, 0.723 mmol) and DIPEA (187 mg, 1.69 mmol) were added. The mixture was stirred for 15 h at rt. The mixture was treated with water and extracted with EA. The organic phase was concentrated and the residue was purified by prep-HPLC to afford compound **902** (30 mg, 25.4 %). +ESI-MS:*m/z* 429.0 [*M*+*H*]⁺.

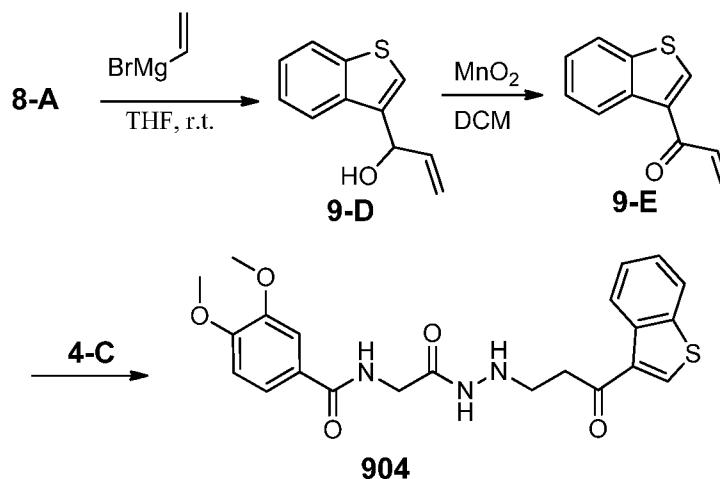
EXAMPLE 9-2 **Preparation of Compound 903**



[0625] To a solution of compound **401** (94.2 mg, 0.237 mmol) in anhydrous MeOH (10 mL) was added 10% Pd/C (20 mg) under a nitrogen atmosphere. The nitrogen atmosphere was replaced with a hydrogen atmosphere and then the mixture was stirred at rt for 4 h. The hydrogen atmosphere was replaced with nitrogen and then the mixture was

filtered through a pad of celite. The filtrate was concentrated under reduced pressure to afford compound **903** as a white solid (92.4 mg, 97.6%). +ESI-MS:m/z 400.0[M+H]⁺.

EXAMPLE 9-3
Preparation of Compound 904

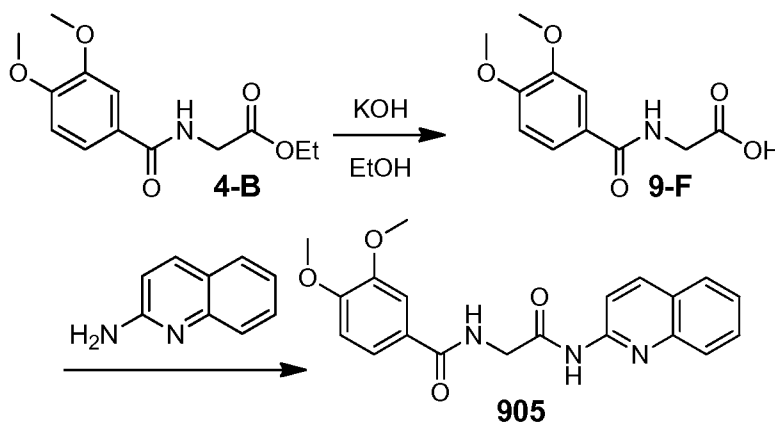


[0626] To a solution of benzo[*b*]thiophene-3-carboxaldehyde (**8-A**) (3.22 g, 20 mmol) in THF (20 mL), vinyl magnesium bromide (20 mmol, 1M in Et₂O) was added dropwise at rt. The mixture was stirred for 2 h at rt. The mixture was treated with aqueous NH₄Cl and extracted with EA. The organic phase was concentrated and the residue was purified by column chromatography on silica gel (PE:EA = 50:1) to afford **9-D** (2.50 g, 65.7 %).

[0627] To a solution of **9-D** (1 g, 5.26 mmol) in DCM (10 mL), MnO₂ (2.7 g, 31 mmol) was added at rt. The reaction solution was stirred for 15 h at 40°C. The solid was removed by filtration and the organic phase was concentrated. The residue was purified by column chromatography on silica gel (PE:EA=100:1-20:1) to afford **9-E** (250 mg, 25.3 %).

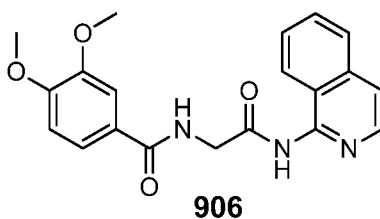
[0628] To a mixture of **9-E** (100 mg, 0.532 mmol) in ethanol (5 mL), **4-C** (134 mg, 0.532 mmol) was added. The mixture was stirred for 2 h at rt. The mixture was filtrated and the solid was collected and washed with ethanol to afford compound **904** (30 mg, 14%). +ESI-MS:m/z 442.1 [M+H]⁺.

EXAMPLE 9-4
Preparation of Compound 905



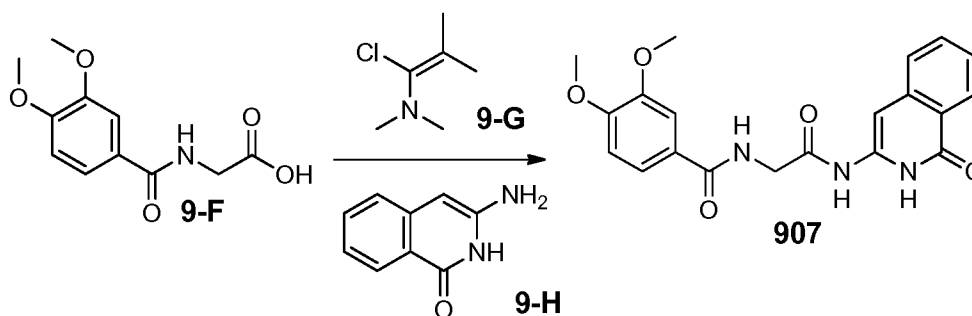
[0629] To a solution of **4-B** (16 g, 60 mmol) in EtOH (300 mL) was added KOH (32 g, 570 mmol) in H₂O (300 mL). The mixture was stirred for 2 h at 70°C. The mixture was concentrated, acidified with 2N HCl to form a precipitate. The precipitate was collected by filtration and washed with H₂O to afford **9-F** (13 g, 80 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.28-12.43 (br, 1H), 8.71-8.68 (br, 1H), 7.51-7.49 (m, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.91 (d, *J* = 5.8 Hz, 2H), 3.80 (s, 6H).

[0630] A mixture of **9-F** (0.8 g, 3.3 mmol) and acetic anhydride (5 mL) was heated 70°C for 2 h and then the acetic anhydride was removed to afford the mixed anhydride. The anhydride was dissolved in THF and treated with quinolin-2-amine (50 mg, 0.33 mmol). The mixture was stirred for 10 h at 70°C. The solvent was removed to afford a residue and the residue was purified by prep-HPLC to afford compound **905** (10 mg, 10 %). +ESI-LCMS: *m/z* 366.0 [M+H]⁺.



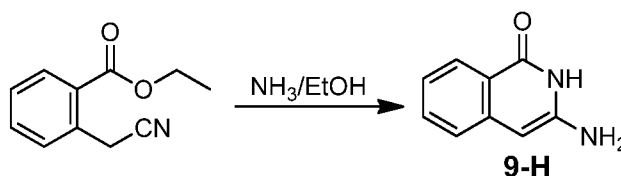
[0631] Compound **906** was obtained following the procedure for obtaining compound **905** using isoquinolin-1-amine in place of quinolin-2-amine. Compound **906** was obtained as a white solid (12 mg, 36.1%). +ESI-MS: *m/z* 366.0 [M+H]⁺.

EXAMPLE 9-5
Preparation of Compound 907



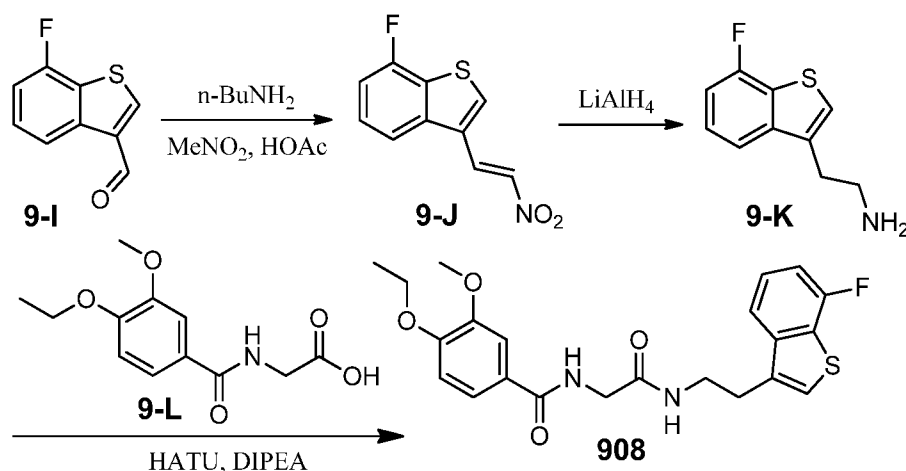
[0632] To a solution of **9-F** (150 mg, 0.63 mmol) in anhydrous DCM (3 mL) was added 1-chloro-*N,N*,2-trimethyl-1-propenylamine (**9-G**) (101 mg, 0.69 mmol) at 0 °C under N₂. The solution was warmed to rt and stirred for 30 mins. Subsequently, 3-aminoisoquinolin-1(2*H*)-one (**9-H**) (60 mg, 0.38 mmol) in dry DMF (1 mL) and pyridine (0.5 mL) was added. The mixture was stirred at rt for 10 h. The mixture was concentrated and the crude material was purified by pre-HPLC to afford the compound **907** (15 mg, 10 %). ESI-LCMS: *m/z* 382 [M+H]⁺.

EXAMPLE 9-6
Preparation of Compound 9-H



[0633] A mixture of ethyl 2-cyanomethylbenzoate (0.8 g, 4 mmol) and NH₃/EtOH (30 mL) in a sealed tube was heated to 50°C for 3 days and then cooled to rt. A precipitate was formed and was collected to afford 3-aminoisoquinolin-1(2*H*)-one (**9-H**) (100 mg, 15%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.66-10.44 (br, 1H), 7.89-7.87 (m, 1H), 7.40-7.36 (m, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 6.99-6.95 (m, 1H), 5.54 (br, 1H), 5.43 (s, 1H).

EXAMPLE 9-7
Preparation of Compound 908

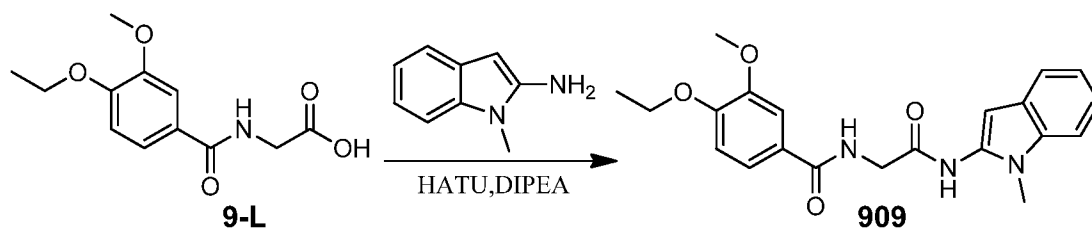


[0634] A mixture of 7-fluorobenzo[b]thiophene-3-carboxaldehyde (**9-I**) (1.0 g, 5.6 mol), $n\text{-BuNH}_2$ (0.49 g, 6.7 mmol) and MeNO_2 (1.1 g, 18 mmol) in HOAc (6 mL) was heated to 80°C for 3 h. The mixture was poured into H_2O and extracted with DCM. The organic layer was removed. The crude product was recrystallized from EtOH to afford **9-J**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.27 (d, $J = 13.8$ Hz, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 7.74 (d, $J = 5.4$ Hz, 1H), 7.54-7.49 (m, 1H), 7.21-7.17 (m, 1H).

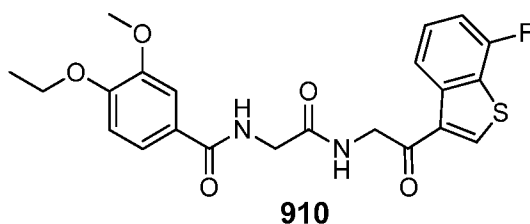
[0635] To a suspension of LiAlH_4 (860 mg, 22.6 mmol) in dry THF (6 mL) was added a solution of **9-J** (900 mg, 45 mmol) in dry THF (3 mL) under N_2 . The mixture was refluxed for 16 h, and then treated with 50% NaOH . The aqueous mixture was extracted with EA. The combined organic phase was dried, and concentrated to afford crude **9-K** used directly for next step without purification.

[0636] To a solution of 2-(4-ethoxy-3-methoxybenzamido)acetic acid (**9-L**) (500 mg, 2.0 mmol), HATU (1.2 g, 3.2 mmol) and DIPEA (700 mg, 5.4 mmol) in anhydrous DCM (15 mL) was added **9-K** (390 mg, 2.0 mmol). The mixture was stirred for 10 h and then diluted with 1.0 N aqueous NaHCO_3 solution, and extracted with DCM. The combined organic phase was dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by recrystallization to afford the compound **908** (200 mg, 50%). ESI-LCMS: m/z 431 $[\text{M}+\text{H}]^+$.

Example 9-8
Preparation of Compound 909

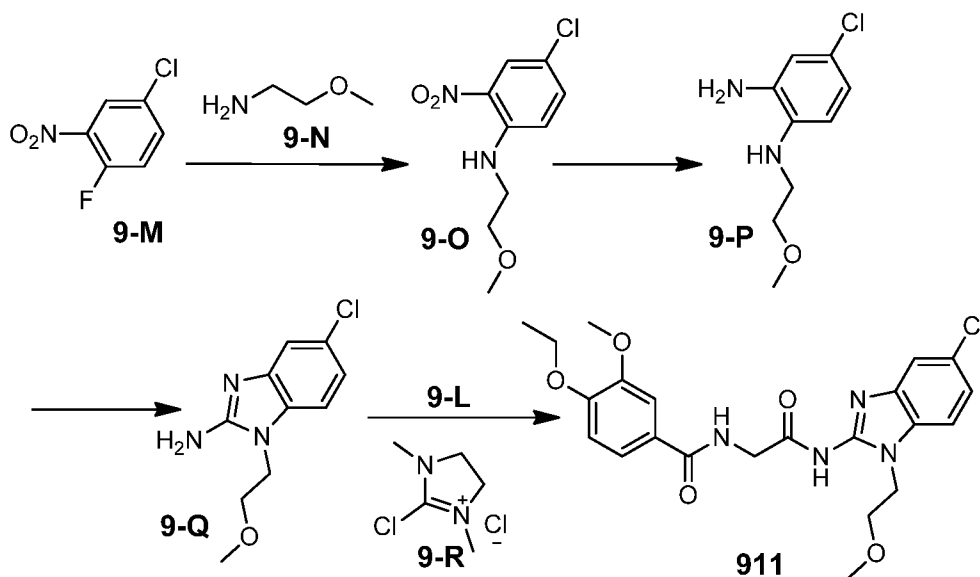


[0637] To a solution of 2-(4-ethoxy-3-methoxybenzamido)acetic acid (**9-L**) (152 mg, 0.6 mmol) in DCM (5 mL) was added HATU (380 mg, 1 mmol) and DIPEA (162 mg, 1.25 mmol), the mixture was stirred at rt, then was added 1-methyl-1*H*-indol-2-amine (110 mg, 0.5 mmol). The mixture was stirred at rt for additional 15 h. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by HPLC to afford compound **909** (35 mg, 18.4%) as a white solid. ESI-LCMS: m/z 382.0 $[M+H]^+$.



[0638] Compound **910** was obtained following the procedure for obtaining compound **909** using 2-amino-1-(7-fluorobenzo[*b*]thiophen-3-yl)ethanone in place of 1-methyl-1*H*-indol-2-amine. Compound **910** was obtained as a white solid (37 mg, 31.1%). +ESI-MS: m/z 445.0 $[M+H]^+$.

EXAMPLE 9-9
Preparation of Compound 911



[0639] To a solution of 4-chloro-1-fluoro-2-nitrobenzene (**9-M**) (10 g, 57 mmol) in DMF (100 mL), K_2CO_3 (11.8 g, 85 mmol) was added. Then 2-methoxyethanamine (**9-N**) (5.12 g, 68.3 mmol) was added. The solution was stirred for 15 h at rt and then poured into water and extracted with EA. The organic phase was concentrated to afford crude **9-O** (12 g, 91.5%).

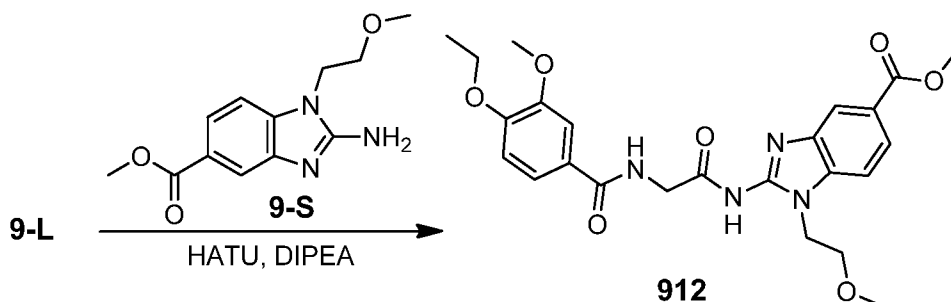
[0640] To a solution of **9-O** (6 g, 26 mmol) in DCM/MeOH (10/50 mL), $NiCl_2 \cdot 6H_2O$ (7.44 g, 31 mmol) was added. Then $NaBH_4$ (5.28 g, 0.138 mol) was added in portions until the solution turned dark. The mixture was treated with aqueous $NaHCO_3$ and extracted with EA. The organic phase was concentrated to afford crude **9-P** (5 g, 96.15%).

[0641] To a solution of **9-P** (3 g, 14.9 mmol) in ethanol, BrCN was added slowly at rt. The mixture was stirred for 15 h at rt. The mixture was treated with aqueous $NaHCO_3$ and extracted with EA. The organic phase was concentrated and the residue was recrystallized (PE:EA = 1:1) to afford **9-Q** (2g, 59.7%).

[0642] To a mixture of **9-Q** (112 mg, 0.442 mmol) in DMF (2 mL), 2-(4-ethoxy-3-methoxybenzamido)acetic acid (**9-L**) (100 mg, 0.442 mmol) and TEA (134 mg, 1.32 mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (**9-R**) (150 mg, 0.884 mmol) were added. The mixture was stirred for 15 h under rt. The mixture was washed with water and

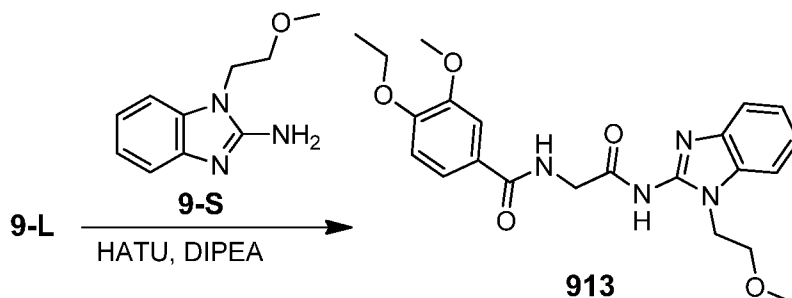
extracted with EA. The organic phase was concentrated and the residue was purified by prep-HPLC to afford compound **911** (2 mg, 1.0%). +ESI-MS:m/z 461.0 [M+H]⁺.

EXAMPLE 9-10
Preparation of Compound 912

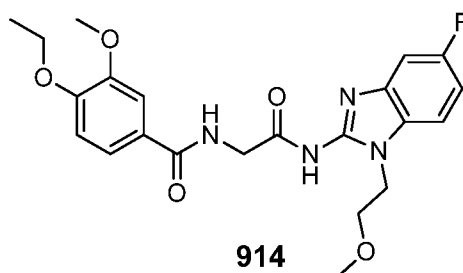


[0643] To a solution of 2-(4-ethoxy-3-methoxybenzamido)acetic acid (**9-L**) (500 mg, 2.0 mmol), HATU (1.2 g, 3.2 mmol) and DIPEA (700 mg, 5.4 mmol) in anhydrous DCM (15 mL) was added methyl 2-amino-1-(2-methoxyethyl)-1H-benzo[d]imidazole-5-carboxylate (**9-S**) (491 mg, 2.0 mmol). The solution was stirred for 10 h and then diluted with 1.0 N aqueous NaHCO₃ solution, extracted with DCM. The combined organic phase was dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC to afford compound **912** (100 mg, 20%). +ESI-MS:m/z 485.1 [M+H]⁺.

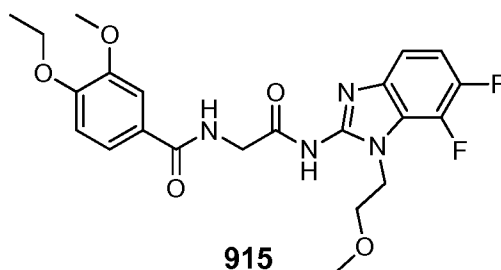
EXAMPLE 9-11
Preparation of Compound 913



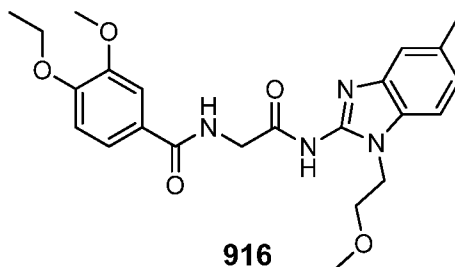
[0644] To a solution of 2-(4-ethoxy-3-methoxybenzamido)acetic acid (**9-L**) (600 mg, 2.4 mmol), HATU (1.3 g, 3.4 mmol) and DIPEA (780 mg, 6.0 mmol) in anhydrous DCM (15 mL) was added **9-S** (453 mg, 2.4 mmol). The solution was stirred for 10 h and then diluted with 1.0 N aqueous NaHCO₃ solution, extracted with DCM. The combined organic phase dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC to afford compound **913** (100 mg, 20%). ESI-LCMS: m/z 427.0 [M+H]⁺.



[0645] Compound **914** was obtained following the procedure for obtaining compound **911** modified as appropriate using 4-fluoro-2-nitroaniline. Compound **914** was obtained as a white solid (22 mg, 15.6%). ESI-LCMS: m/z 445.1 $[M+H]^+$.

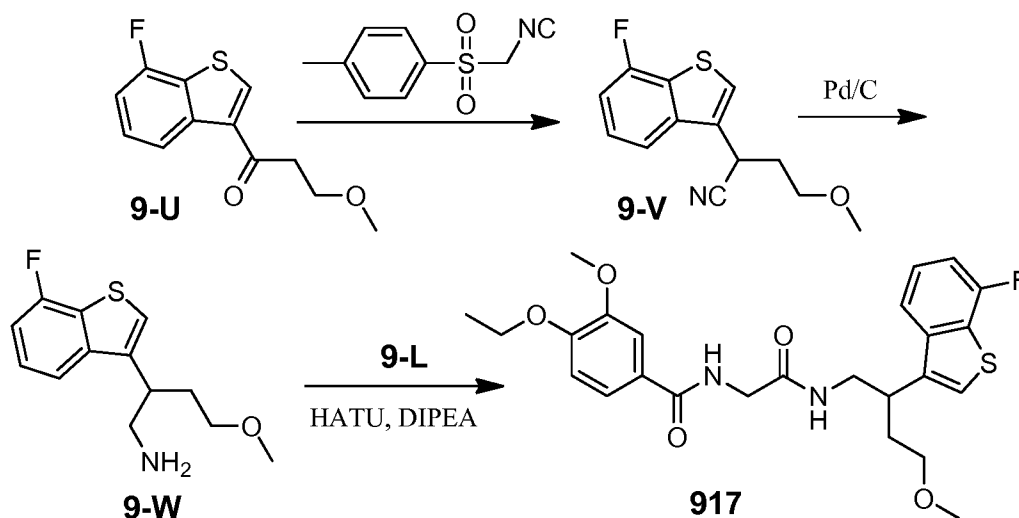


[0646] Compound **915** was obtained following the procedure for obtaining compound **911** modified as appropriate using 2,3-difluoro-6-nitroaniline. Compound **915** was obtained as a white solid (35 mg, 18.8%). ESI-LCMS: m/z 463.2 $[M+H]^+$.



[0647] Compound **916** was obtained following the procedure for obtaining compound **911** using 1-(2-methoxyethyl)-5-methyl-1*H*-benzo[*d*]imidazol-2-amine in place of **9-Q**. Compound **916** was obtained as a white solid (36 mg, 19.6%). ESI-LCMS: m/z 441.5 $[M+H]^+$.

EXAMPLE 9-12
Preparation of Compound 917

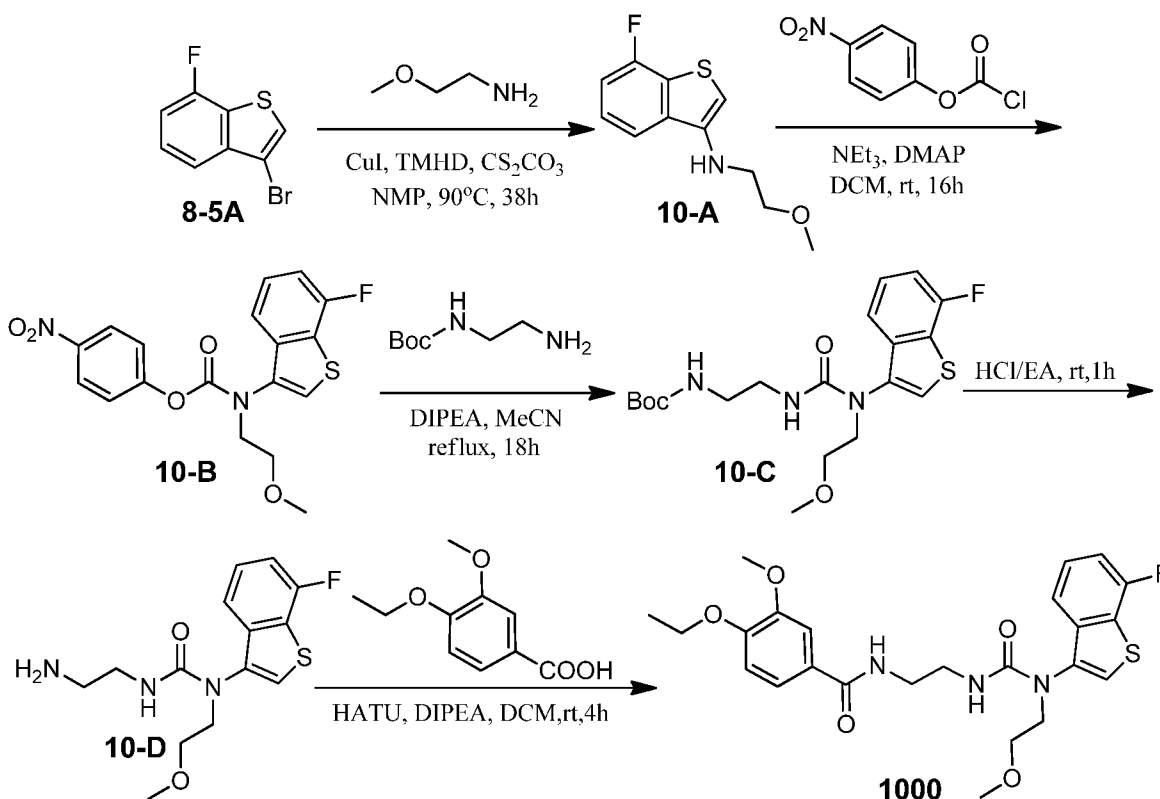


[0648] Solid t-BuOK was added to a stirred and cooled solution of **9-U** (500 mg, 2.1 mmol) and tosylmethyl isocyanide (550 mg, 2.8 mmol) in a mixture of dioxane and EtOH (v/v = 10:1) while keeping the temperature between 0°C and 5°C. The solution was stirred at rt for 2 h. The mixture was poured in H₂O and extracted with EA. The organic layer was dried and concentrated. The residue was purified by TLC to afford **9-V**. ¹H NMR (400 MHz, DMSO-d₆) δ 7.96 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.55-7.49 (m, 1H), 7.35-7.30 (m, 1H), 4.73-4.69 (m, 1H), 3.52-3.39 (m, 2H), 3.26 (s, 1H), 2.33-2.17 (m, 2H).

[0649] A vessel under N₂ was charged with **9-V** (150 mg, 0.60 mmol), Pd/C (80 mg) in ethanol (5 mL) and HCl (0.2 mL). The vessel was placed under 1 atm of H₂ and then stirred at rt for 5 h. The solid was removed by filtration through a pad of celite and the filtrate was concentrated to afford crude **9-W** used directly in next step without further purification.

[0650] To a solution of 2-(4-ethoxy-3-methoxybenzamido)acetic acid (**9-L**) (80 mg, 0.32 mmol), HATU (160 mg, 0.42 mmol) and DIPEA (103 mg, 0.8 mmol) in anhydrous DCM (3 mL) was added **9-W** (80 mg, 0.32 mmol). The mixture was stirred for 10 h and then diluted with a 1.0 N aqueous NaHCO₃ solution, and extracted with EA. The combined organic phase was dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC to afford the compound **917** (5 mg). ESI-LCMS: m/z 489.1 [M+H]⁺.

EXAMPLE 10
Preparation of Compound 1000



[0651] To a mixture of 3-bromo-7-fluorobenzo[b]thiophene (**8-5A**) (1.13 g, 4.9 mmol), CuI (0.140 g, 0.15eq.), TMHD (0.271 g, 0.30eq.) and Cs_2CO_3 (3.19 g, 2 eq.) in NMP (10 mL) was added 2-methoxyethanamine (2.2 g, 6 eq.). The mixture was stirred at 90°C for 38 h. The mixture was diluted with water and extracted with EA, the organic layer was collected and dried over anhydrous MgSO_4 . After filtration, the solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **10-A** as a white solid (0.741g, 67.2%). +ESI-MS: m/z 225.9 $[\text{M}+\text{H}]^+$.

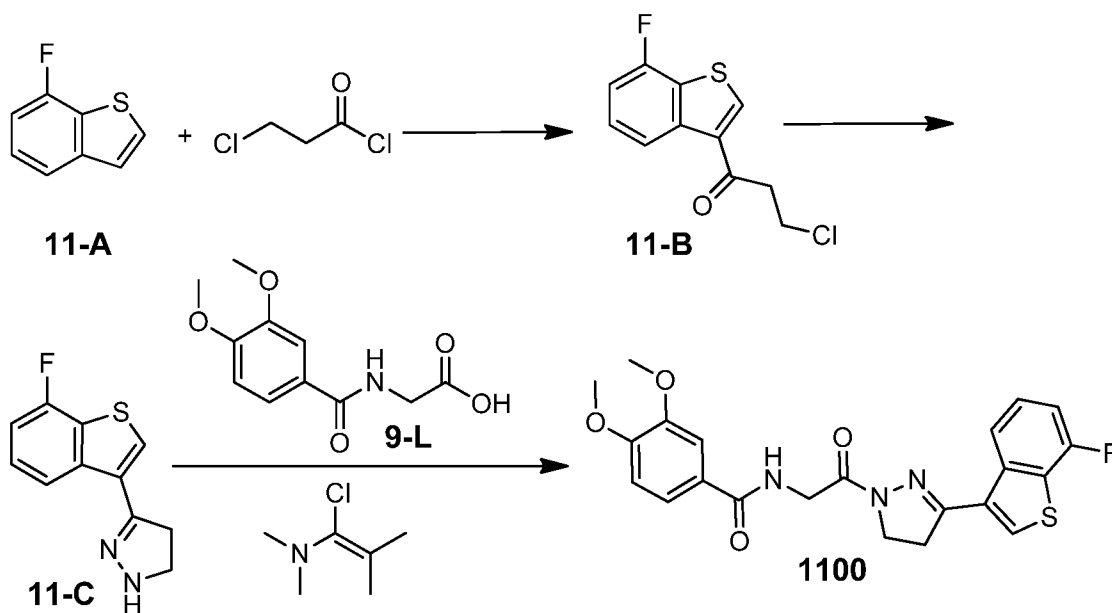
[0652] To a solution of **10-A** (150 mg, 0.67 mmol), triethylamine (101 mg, 1.5eq.), and DMAP (16 mg, 0.2 eq.) in DCM (10 mL) was added 4-nitrophenyl chloroformate (201 mg, 1.5eq.). The mixture was stirred at rt for 16 h. The mixture was diluted with water and extracted with EA, the organic layer was collected and dried over anhydrous MgSO_4 . After filtration, the solvent was removed and the residue was purified by silica gel column (PE/EA = 10/1 to 3/1) to afford **10-B** as a white solid (220 mg, 84.6%). +ESI-MS: m/z 390.8 $[\text{M}+\text{H}]^+$.

[0653] To a solution of **10-B** (220 mg, 0.56 mmol) and DIPEA (218 mg, 3.0 eq.) in MeCN (20 mL) was added tert-butyl (2-aminoethyl)carbamate (451 mg, 5.0eq.). The mixture was heated to reflux for 18 h. The mixture was allowed to cool to rt and then diluted with water. The aqueous mixture was extracted with EA, the organic layer was collected and dried over anhydrous MgSO_4 . After filtration, the solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **10-C** as a white solid (200 mg, 86.2%). +ESI-MS: m/z 412.0 $[\text{M}+\text{H}]^+$.

[0654] Compound **10-C** (200 mg, 0.49 mmol) was added to a HCl/EA (50 mL) solution. The mixture was stirred at rt for 1 hour. The formed precipitate was filtered and washed with EA (10 mL $\times$ 3) and then dried to afford **10-D** as a white solid (147 mg, 97%). +ESI-MS: m/z 311.9 $[\text{M}+\text{H}]^+$.

[0655] To a solution of 4-ethoxy-3-methoxybenzoic acid (93 mg, 0.47 mmol) in DMF (6 mL) was added HATU (357 mg, 2 eq.) and DIPEA (243 mg, 4 eq.), the mixture was stirred at rt for 30 mins, the mixture was then treated with **10-D** (147 mg, 0.47 mmol). The mixture was stirred at rt for another 4 h. The mixture was washed with water and the organic layer was collected. The solvent was removed and the residue was purified by prep-HPLC to afford compound **1000** as a white solid (42 mg, 18.2%). +ESI-MS: m/z 490.2 $[\text{M}+\text{H}]^+$.

EXAMPLE 11 Preparation of Compound 1100

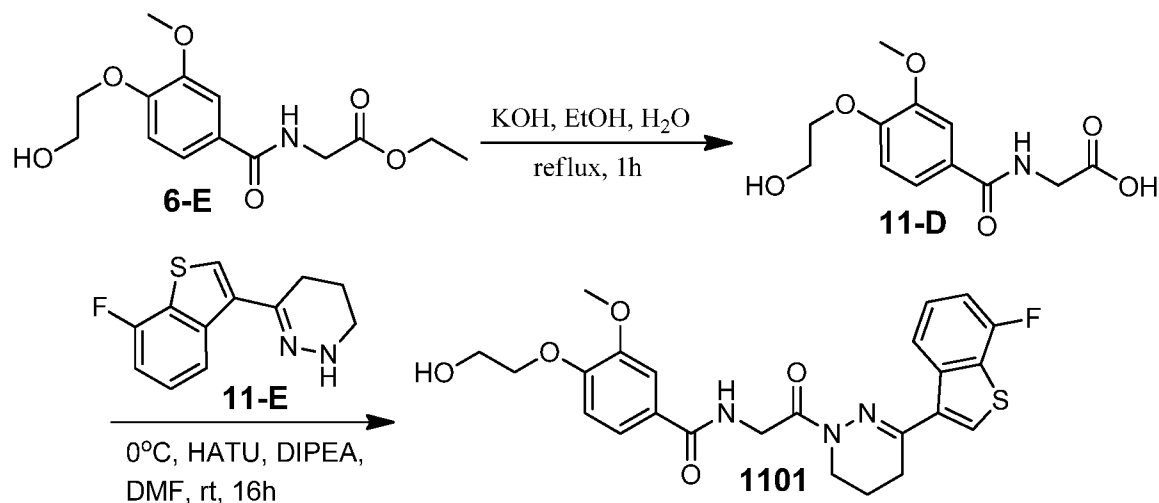


[0656] To a mixture of aluminum trichloride (2.66 g, 20 mmol) in dry DCM (10 mL) cooled at 0°C under N₂, was added a solution of 7-fluorobenzo[*b*]thiophene (**11-A**) (3.044 g, 20 mmol) and then 3-chloropropanoyl chloride (2.53 g, 20 mmol) in dry DCM (10 mL) was slowly added. The mixture was stirred at rt for 1 hour. The mixture was cooled to -78 °C (acetone-carbon dioxide bath) and a solution of 96% sulphuric acid (1 mL) and water 15 mL was slowly added. The organic layer was decanted, washed with water and dried over anhydrous MgSO₄. After filtration, the solvent was removed and the residue was purified by silica gel column (PE/EA = 20/1 to 8/1) and then re-crystallization in PE/EA (30:1) to afford **11-B** as a white solid (1.654 g, 34%). +ESI-MS:m/z 243.0 [M+H]⁺.

[0657] To a solution of **11-B** (300 mg, 1.2 mmol) in iso-propyl alcohol (10 mL) was added N₂H₄.xH₂O (119 mg, 3.6 mmol). The mixture was heated to reflux for 1 hour. Then the mixture was allowed to cool to rt and the solvent was evaporated to afford crude **11-C** (270 mg, 99.3%), which was used for next step directly without further purification.

[0658] To a solution of 2-(3,4-dimethoxybenzamido)acetic acid (**9-L**) (586 mg, 2.45 mmol) in dry DCM (6 mL) cooled at 0°C and under N₂, was added 1-chloro-*N,N*,2-trimethyl-1-propenylamine (360 mg, 2.70 mmol). The mixture was stirred at rt for 1 hour. The mixture was treated with crude **11-C** (270 mg) in dry DCM (6 mL) and the mixture was allowed to stir at rt for one more hour. The mixture was diluted with water and extracted with EA. The organic layer was collected and dried over anhydrous MgSO₄. After filtration, the solvent was removed and the residue was purified by silica gel column (DCM/MeOH = 40/1 to 10/1) to afford compound **1100** as a white solid (279 mg, 51.6%). +ESI-LCMS: m/z 442.1 [M+H]⁺.

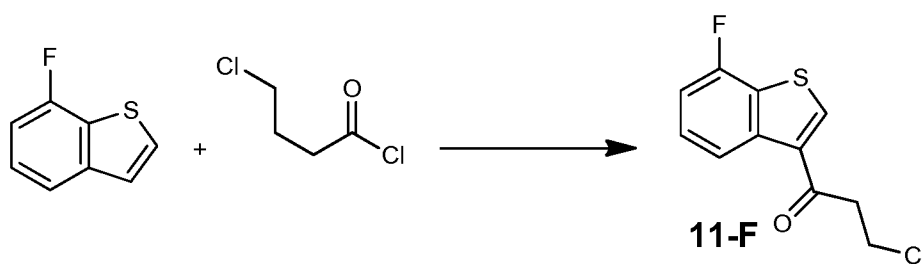
EXAMPLE 11-1
Preparation of Compound 1101



[0659] To a solution of ethyl 2-(4-(2-hydroxyethoxy)-3-methoxybenzamido)acetate (**6-E**) (2.00 g, 6.73 mmol) in EtOH (30 mL) was added a solution of KOH (4.48 g, 80 mmol) in H₂O (10 mL). The mixture was heated to reflux for 1 hour, then was cooled down to rt and diluted with H₂O (50 mL). The EtOH was removed and the remaining aqueous mixture was acidified with HCl aq. to adjust pH to 4-5 at 0°C. A white precipitate was formed. The precipitate was filtered and the residue was washed with EtOH (6 mL × 3) to afford 2-(4-(2-hydroxyethoxy)-3-methoxybenzamido)acetic acid (**11-D**) as a white component (0.50 g, 27.6%).

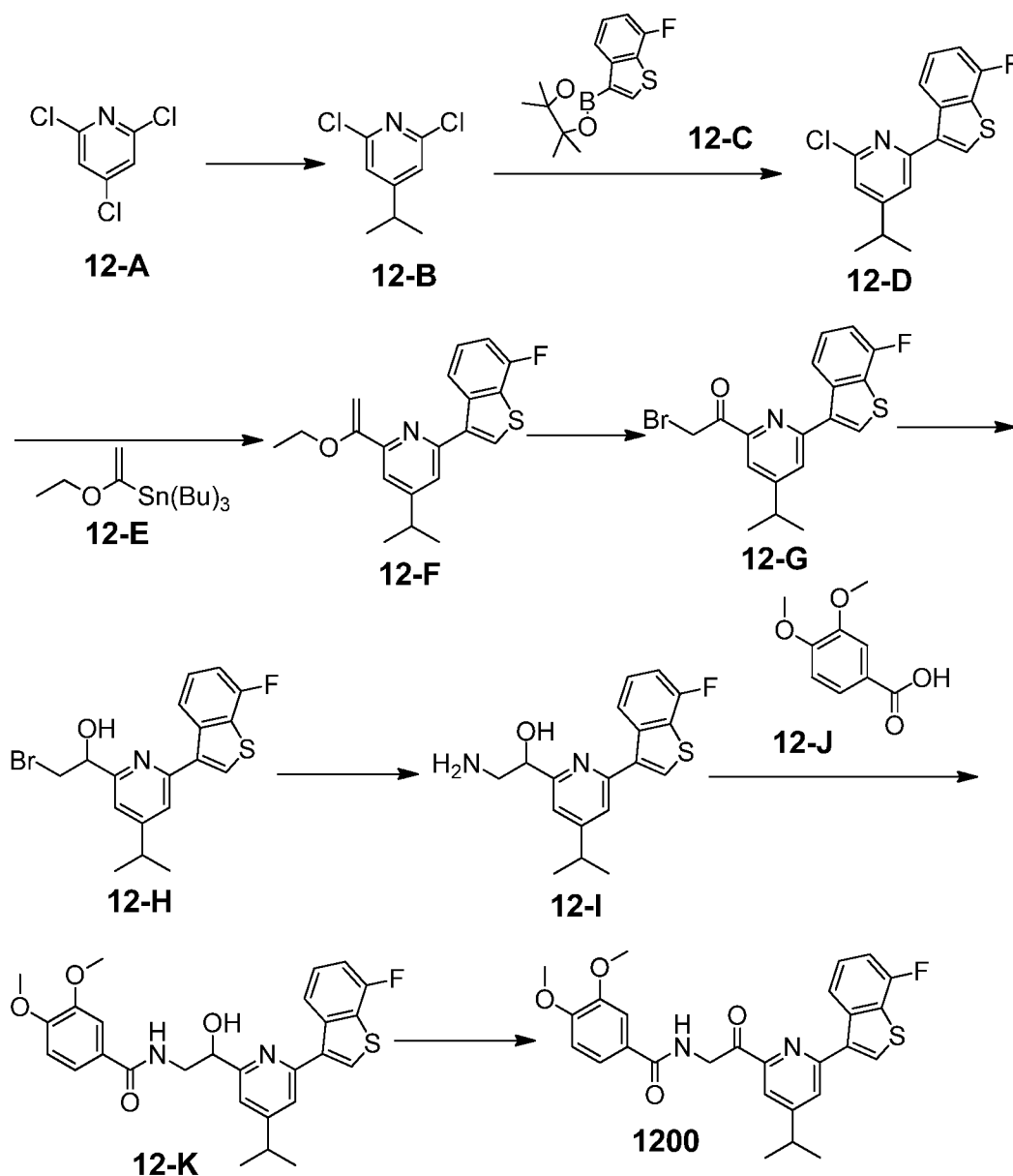
[0660] To a solution of 2-(4-(2-hydroxyethoxy)-3-methoxybenzamido)acetic acid (**11-D**) (34 mg, 1.28 mmol) and DIPEA (112 mg, 0.87 mmol) in DMF (2 mL) at 0°C was added HATU (654 mg, 2.0 eq.). The mixture was stirred at 0 °C for 30 mins, then was added 3-(7-fluorobenzo[b]thiophen-3-yl)-1,4,5,6-tetrahydro-pyridazine (**11-E**) (200 mg, 0.86 mmol). The mixture was stirred at rt for another 16 h. The mixture was diluted with water and extracted with EA. The organic layer was collected and dried over anhydrous MgSO₄. After filtration, the solvent was removed and the residue was purified by prep-TLC (EA) and recrystallization from EA. Compound **1101** was obtained as a white solid (91.36 mg, 22.1%). +ESI-LCMS:m/z 486.1[M+H]⁺.

EXAMPLE 11-2
Preparation of Compound 11-F



[0661] Compound **11-F** was obtained following the procedure for obtaining **11-B** using 4-chlorobutanoyl chloride in place of 3-chloropropanoyl chloride. Compound **11-F** was obtained as a brown solid (1.067 g, 37.3%).

EXAMPLE 12
Preparation of Compound 1200



[0662] To a mixture of **12-A** (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 **12-B** as a colorless solid (2.4 g, 63.5%). +ESI-MS: m/z 190.1 [M + H]⁺.

[0663] To a mixture of **12-B** (1 g, 5.29 mmol) and **12-C** (1.03 g, 5.29 mmol) in DMF (30 mL) were added Pd(dppf)Cl₂ (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 rt, diluted with EA and separated from the water layer. The EA solution was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **12-D** as a colorless solid (0.5 g, 31%). +ESI-MS: m/z 306.0 [M + H]⁺.

[0664] To a mixture of **12-D** (900 mg, 2.95 mmol), **12-E** (1.07 g, 2.95 mmol) and KF (0.684 g, 11.8 mmol) in DMF (10 mL) was added Pd(dppf)Cl₂ (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 rt, diluted with EA and H₂O. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to give crude **12-F** (1 g). +ESI-MS: m/z 342.1 [M + H]⁺.

[0665] A mixture of **12-F** (1 g, 2.9 mmol) and NBS (516 mg, 2.9 mmol) in a mixture of THF (10 mL) and H₂O (1 mL) was stirred at rt 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 saturated Na₂S₂O₃ solution, followed by brine. The solution was dried over Na₂SO₄ and evaporated to give crude **12-G** (1 g). +ESI-MS: m/z 392.0 [M + H]⁺.

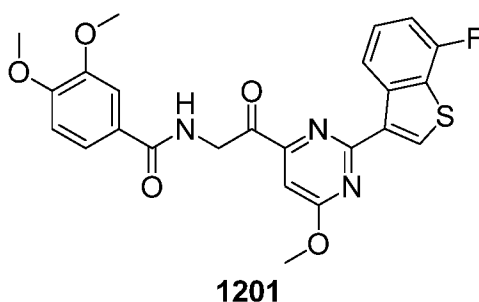
[0666] To a solution of **12-G** (1 g, 2.55 mmol) in a mixture of THF (5 mL) and MeOH (0.5 mL) was added NaBH₄ (193 mg, 5.1 mmol) at 0°C. The mixture was stirred at 0°C for 30 mins with TLC monitoring. The reaction was quenched by the addition of H₂O and extracted with EA. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **12-H** (200 mg, 20%). +ESI-MS: m/z 394.0 [M + H]⁺.

[0667] A mixture of **12-H** (200 mg, 0.50 mmol) and saturated NH₄OH/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 **12-I** (160 mg, 90.0%), which was used for next step directly without purification. +ESI-MS: m/z 331.1 [M + H]⁺.

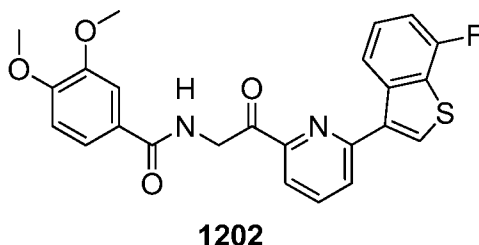
[0668] To a solution of **12-J** (65 mg, 0.363 mmol), HATU (172 mg, 0.45 mmol) and DIPEA (117 mg, 0.909 mmol) in anhydrous DMF (1 mL) was added **12-I** (100 mg 0.303 mmol) at 25°C. The solution was stirred for 10 h at rt. The solution was diluted with 1.0 N aqueous NaHCO₃ solution (40 mL x 2) and extracted with EA (20 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 on a silica gel column to give **12-K** (100 mg, 67.1%). +ESI-MS: m/z 495.1 $[\text{M} + \text{H}]^+$.

[0669] To a mixture of **12-K** (100 mg, 0.203 mmol) in DCM (2 mL) were added DMP (517 mg, 1.4 mmol). The mixture was stirred at rt for 30 mins with TLC monitoring. The solution was quenched using an aqueous NaHCO_3 solution and extracted with EA. The combined organic layers were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by Pre-HPLC(FA) to give compound **1200** as a white solid (30 mg, 30%). +ESI-MS: m/z 493.0 $[\text{M} + \text{H}]^+$.

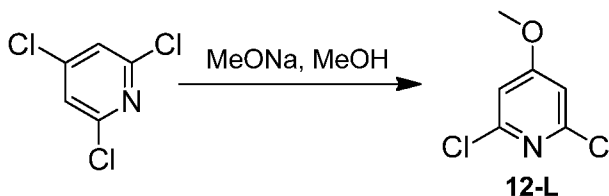


[0670] Compound **1201** was obtained following the procedure for obtaining compound **1200** by using 4-chloro-2-iodo-6-methoxypyrimidine as the starting material. Compound **1201** was obtained as a white solid. +ESI-MS: m/z 482.9 $[\text{M} + \text{H}]^+$.

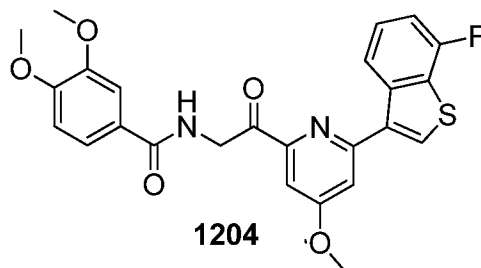


[0671] Compound **1202** was obtained following the procedure for obtaining compound **1200** by using 2,6-dichloropyridine as the starting material. Compound **1202** was obtained as a white solid. +ESI-MS: m/z 450.9 $[\text{M} + \text{H}]^+$.

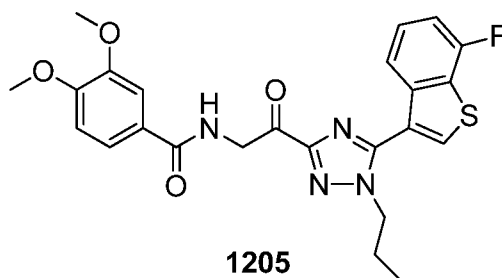
EXAMPLE 12-1 **Preparation of Compound 12-L**



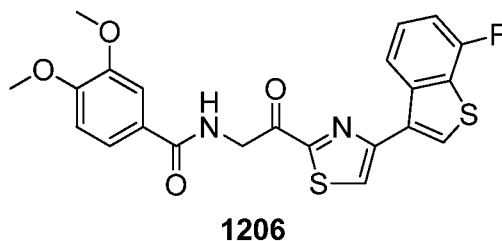
[0672] A solution of 2,4,6-trichloropyridine (6.5 g, 36 mmol) in anhydrous methanol (20 mL) was added MeONa (2.9 g, 54 mmol) at 0°C. The reaction mixture was stirred at rt for 12 h. The reaction was quenched with dry ice, and the mixture was filtered. The solution was concentrated under reduced pressure, and the residue was dissolved in EA. The mixture was washed with water, and the organic layers were dried over NaSO₄. The solvent was concentrated to give **12-L** (4.2 g, 67%).



[0673] Compound **1204** was obtained following the procedure for obtaining Compound **1200** by using **12-L** as the starting material. Compound **1204** was obtained as a white solid. Compound **1204**: +ESI-MS: m/z 496.1 [M + H]⁺.

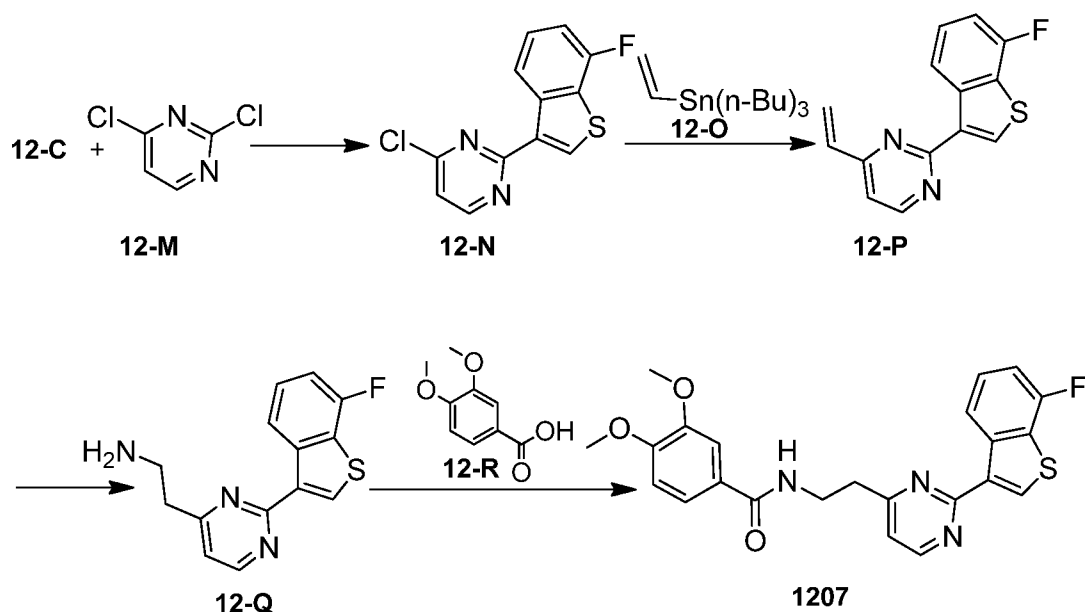


[0674] Compound **1205** was obtained following the procedure for obtaining compound **1200** by using 3,5-dibromo-1-propyl-1H-1,2,4-triazole as the starting material. Compound **1205** was obtained as a white solid. +ESI-MS: m/z 482.9 [M + H]⁺.



[0675] Compound **1206** was obtained following the procedure for obtaining compound **1200** by using 2,4-dibromothiazole as the starting material. Compound **1206** was obtained as a white solid. +ESI-MS: m/z 456.8 [M + H]⁺.

EXAMPLE 12-2
Preparation of Compound 1207



[0676] To a mixture of **12-M** (1.94 g, 20.1 mmol) and **12-C** (3.6 g, 20.0 mmol) in dioxane (20 mL) were added Pd(dppf)Cl₂ (800 mg, 0.94 mmol) and a freshly prepared KF solution (3.6 g in 8 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 6 h. The reaction solution was cooled to rt, diluted with EA and separated from the water layer. The EA solution was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give crude **12-N** (2.8 g), which used for the next step without purification.

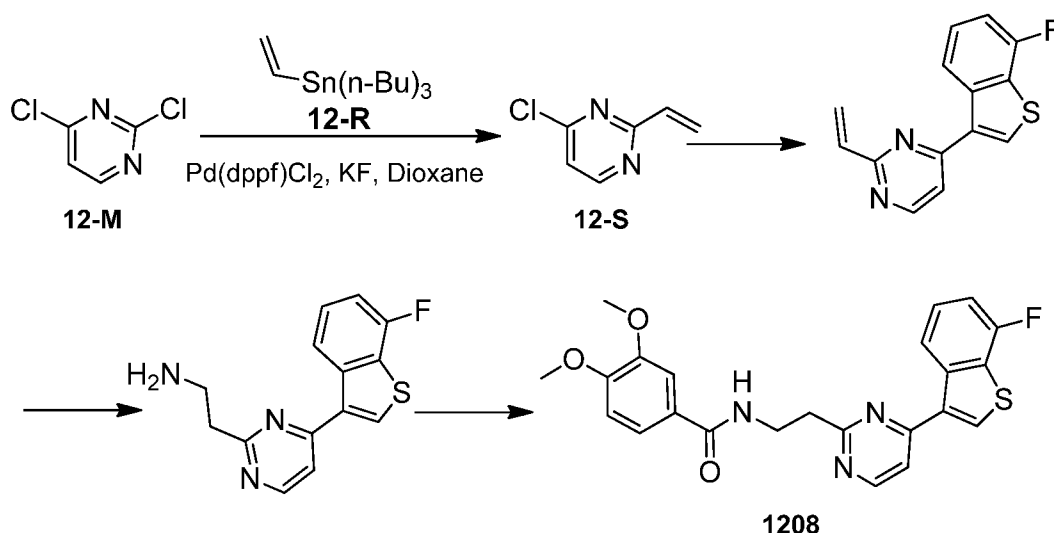
[0677] To a mixture of **12-N** (1.3 g, 5 mmol), **12-O** (1.6 g, 5 mmol) and KF (1.0 g, 16.6 mmol) in DMF (10 mL) were added Pd(dppf)Cl₂ (400 mg, 0.49 mmol). The system was degassed and then charged with nitrogen 3 times. The mixture was stirred under nitrogen at 70°C using an oil bath for 8 h. The reaction solution was cooled to rt, and diluted with water and EtOAc. The EtOAc solution was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give crude **12-P** (0.8 g) as a liquid, which used for the next step without purification.

[0678] To a mixture of **12-P** (0.8 g, 3.1 mmol) in EtOH (5 mL) were added NH₄OH (5 mL) in a sealed tube. The mixture was heated at 70°C for 5 h with TLC

monitoring. The solution was removed under reduced pressure to give crude **12-Q** (0.5 g), which was used for next step directly without purification

[0679] To a solution of **12-R** (91 mg, 0.5 mmol), HATU (250 mg, 0.65 mmol) and DIPEA (200 mg, 1.5 mmol) in anhydrous DCM (3 mL) was added **12-Q** (138 mg 0.5 mmol) at 25°C. The solution was stirred for 8 h at rt. The solution was diluted with 1.0 N aqueous NaHCO₃ solution (40 mL x 2) and extracted with EA (40 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified on a silica gel column (PE:EA=1:2) to give compound **1207** (100 mg) as a white solid. +ESI-MS: m/z 438.1[M+H]⁺.

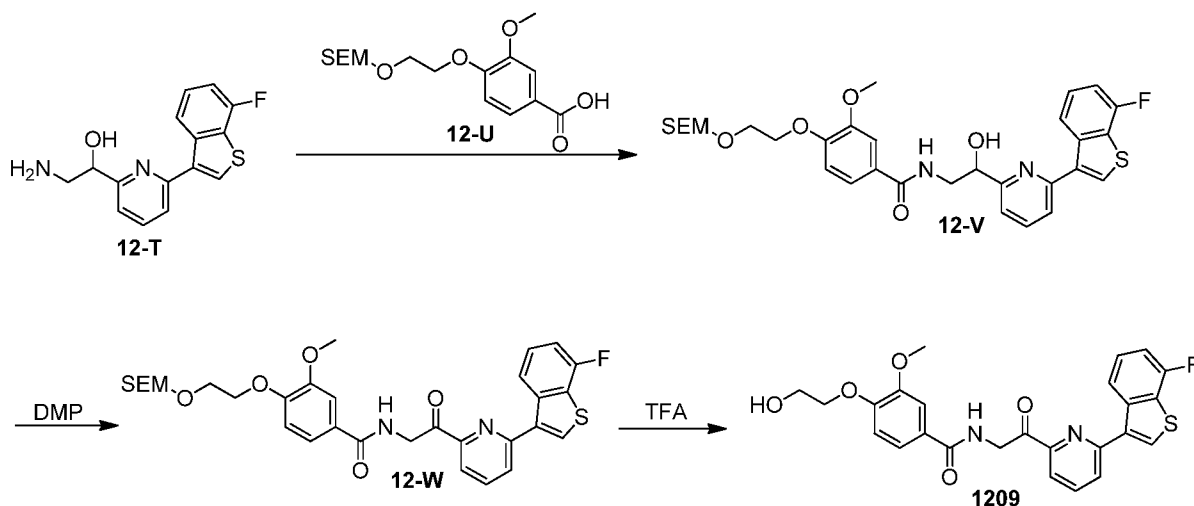
EXAMPLE 12-3 Preparation of Compound 1208



[0680] To a mixture of **12-M** (1.5 g, 10 mmol), **12-R** (3.2 g, 10 mmol) and KF (1.8 g, 30.0 mmol) in DMF (6 mL) was added Pd(dppf)Cl₂ (400 mg, 0.49 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 7 h. The reaction solution was cooled to rt. The mixture was diluted with H₂O and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give crude **12-S** (0.8 g) as a liquid, which was used for the next step without purification.

[0681] Compound **1208** was obtained following the procedure for obtaining compound **1207** by using **12-S**. Compound **1208** was obtained as a white solid. +ESI-MS: m/z 438.1 $[M+H]^+$.

EXAMPLE 12-4
Preparation of Compound 1209

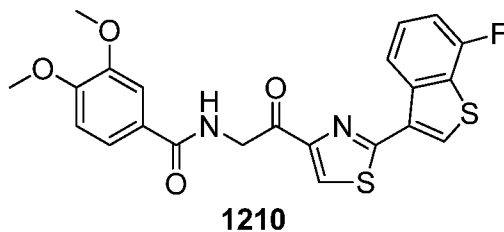


[0682] Compound **12-U** (170 mg, 0.5 mmol), **12-T** (140 mg, 0.5 mmol) and triethylamine (1 mmol) were dissolved in DMF (15 mL). HATU (380 mg, 1 mmol) was added to the solution. After 15-30 mins., the reaction was completed, and a saturated NaCl solution (100 mL) was added. The product was extracted with EtOAc (3×10 mL), and the combined organic phase was washed with 2N HCl solution, 5% NaHCO₃ solution, and brine. The organic phase was dried over MgSO₄, 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 **12-V** as a white solid (240 mg, 80 %). +ESI-MS: m/z 613.2 $[M+H]^+$.

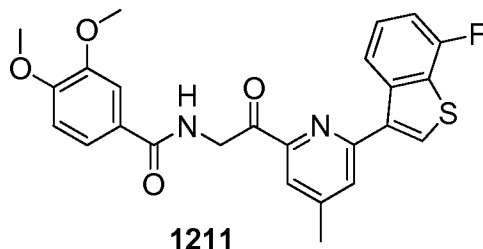
[0683] To a stirred solution of **12-V** (240 mg, 0.4 mmol) in CH₂Cl₂ (10 mL) was added DMP (426 mg, 1.0 mmol), the mixture was stirred at rt until the starting material was consumed completely. The mixture was concentrated to give a residue. Purification of the residue by silica gel column chromatography (PE/EA) gave **12-W** as a solid (185 mg, 75%). +ESI-MS: m/z 611.2 $[M+H]^+$.

[0684] To **12-W** (185 mg, 0.3 mmol) in DCM (10 mL) was added TFA (10 mL). The mixture was stirred for 2 h at rt. The solvent was evaporated under reduced pressure to

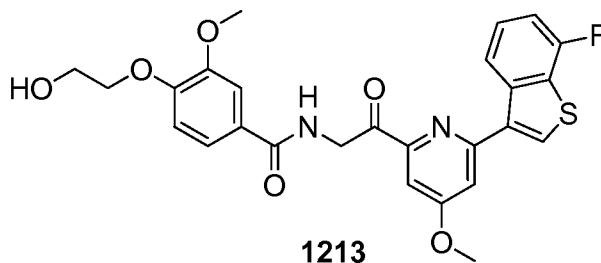
give the crude product as an oil. The crude product was purified by Pre-HPLC to give compound **1209** (28 mg, 30%). +ESI-MS: m/z 480. 9 $[M + H]^+$.



[0685] Compound **1210** was obtained following the procedure for obtaining compound **1200** by using 2,4-dibromothiazole as the starting material. Compound **1210** was obtained as white solid. +ESI-MS: m/z 457.0 $[M + H]^+$.

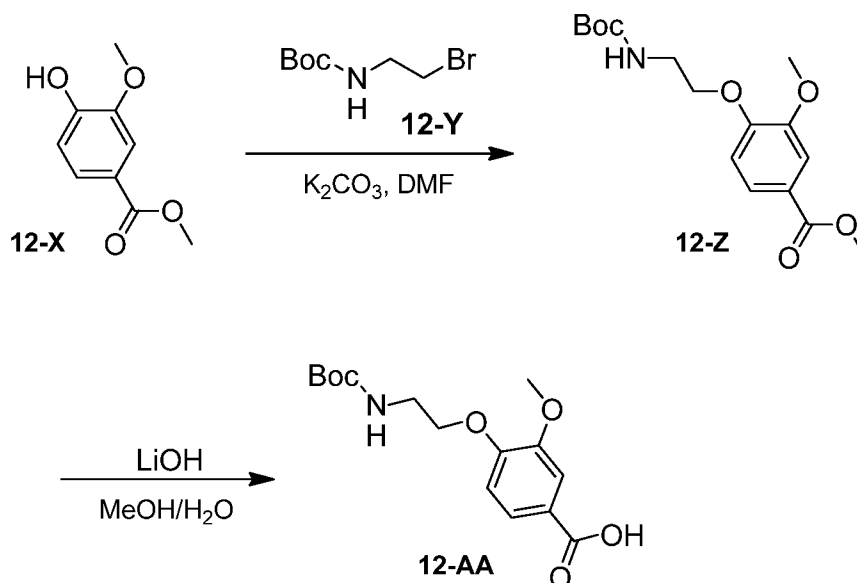


[0686] Compound **1211** was obtained following the procedure for obtaining compound **1200** by using 2,4-dibromothiazole as the starting material. Compound **1211** was each obtained as a white solid. Compound **1211**: +ESI-LCMS: m/z = 464.9 $[M + H]^+$.



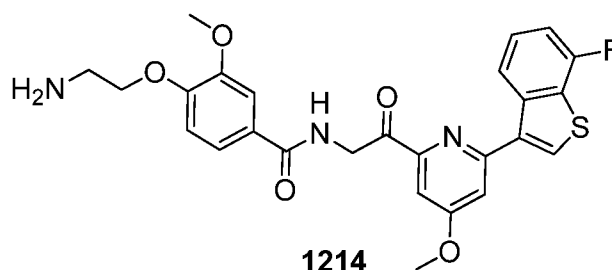
[0687] Compound **1213** was obtained following the procedures for obtaining compounds **1200** and **1209** by using 2,4,6-trichloropyridine as the starting material. Compound **1213** was obtained as a white solid. +ESI-MS: m/z 511. 0 $[M + H]^+$.

EXAMPLE 12-5
Preparation of Compound 12-AA



[0688] To a solution of **12-X** (1.82 g, 10 mmol) and K_2CO_3 (6.9 g, 50 mmol) in DMF (20 mL) was added **12-Y** (4.48 g, 20 mmol) at 25°C. The solution was stirred for 15 h at 90°C. The mixture was diluted with water and extracted with EA. The combined organic phase was dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to give **12-Z** (3.0 g). +ESI-MS: m/z 326.1 $[\text{M} + \text{H}]^+$.

[0689] To a solution of **12-Z** (3.0 g, 9.23 mmol) in MeOH (20 mL) was added LiOH (2.3 g, 95.8 mmol) in H_2O (10 mL). The solution was stirred for 3 h at 50°C. The mixture was concentrated, acidified with 2N HCl solution. The precipitate was collected by filtration and washed with H_2O to give the **12-AA** (2.0 g). ^1H NMR: DMSO (400MHz): δ = 7.54-7.52 (dd, $J=2.0$ Hz, $J=8.4$ Hz, 1 H), 7.44 (s, 1H), 7.04 (d, $J=8.4$ Hz, 1 H), 6.98-6.95 (br s, 1 H), 4.04-4.01 (m, 2 H), 3.79 (s, 3 H), 3.32-3.28 (m, 2 H), 1.37 (m, 9 H).

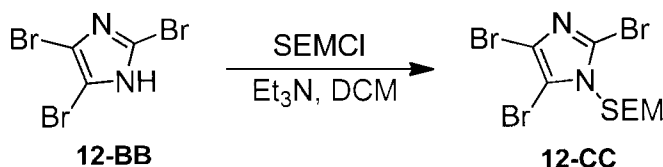


[0690] Compound **1214** was obtained following the procedures for obtaining compounds **1200** and **1209** by using 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)-4-

methoxypyridin-2-yl) ethanol and **12-AA** as the starting materials. Compound **1214** was obtained as a white solid. +ESI-MS: m/z 510.1 $[M+H]^+$.

EXAMPLE 12-6

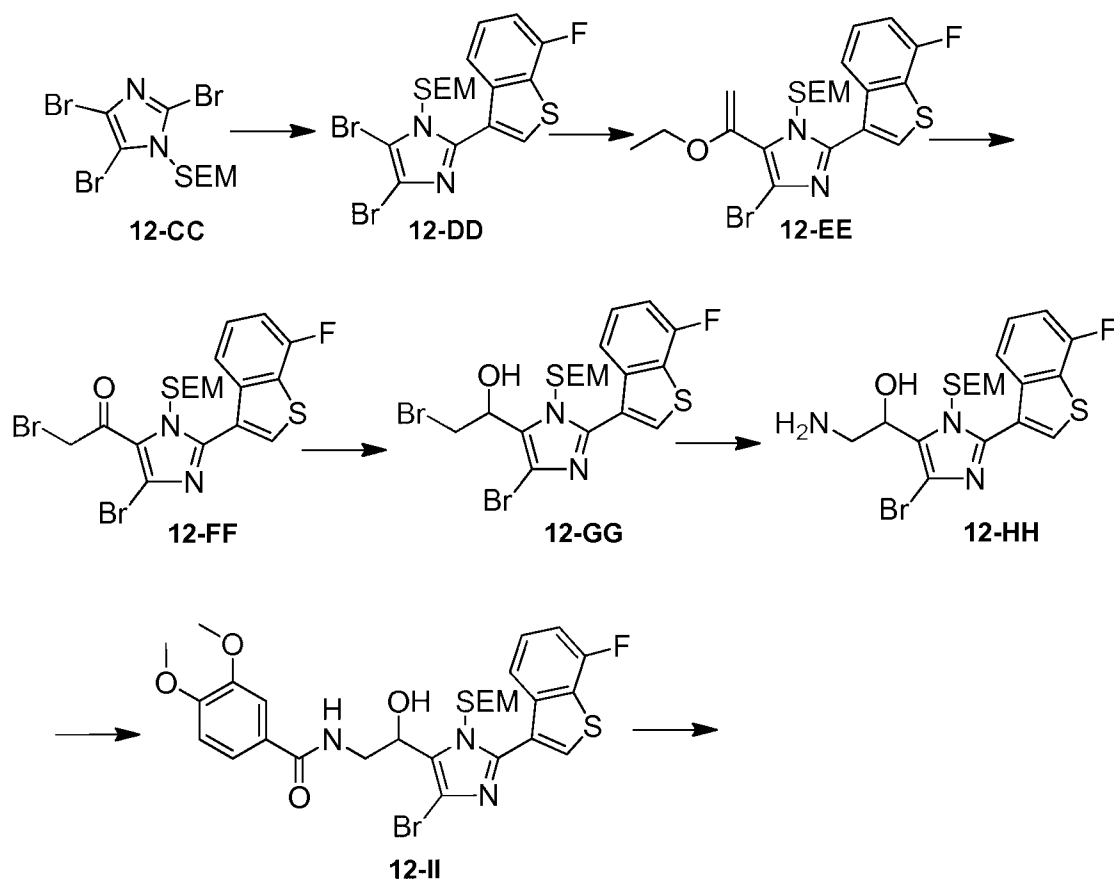
Preparation of Compound 12-CC



[0691] To a solution of **12-BB** (30.0 g, 100.0 mmol) and SEMCl (16.6 g, 100.0 mmol) in DCM (800 mL) were added Et₃N (11 g, 108.9 mmol) at rt. The mixture was stirred at rt for 30 mins with TLC monitoring. The solution was removed under reduced pressure, and the residue was washed with H₂O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give crude **12-CC** (25.0 g), which used for next step without purification.

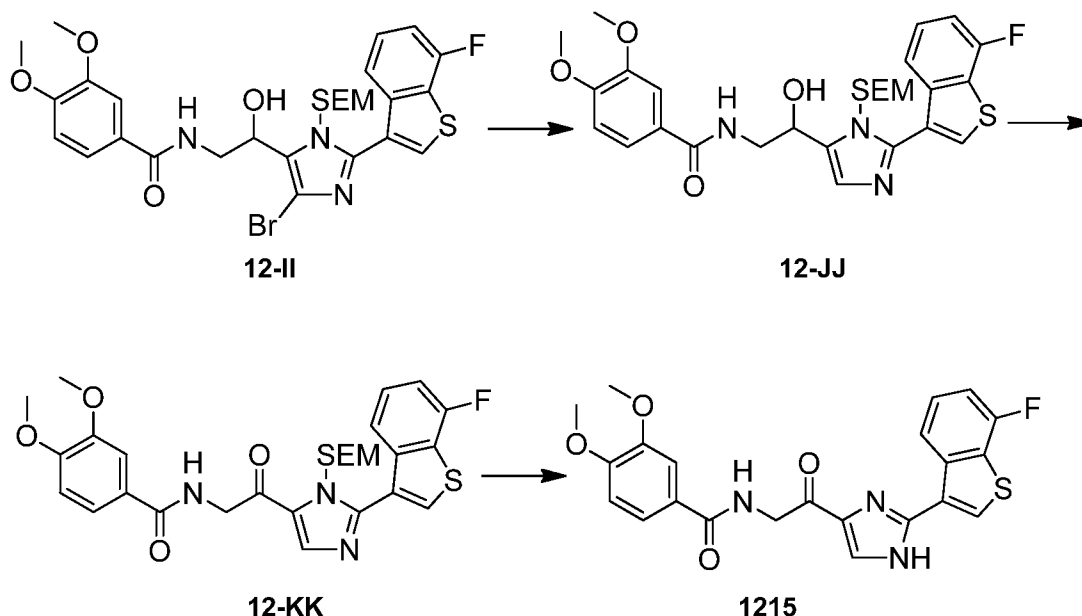
EXAMPLE 12-7

Preparation of Compound 12-II



[0692] Compound **12-II** was obtained following the procedures for obtaining compound **1200** by using **12-CC** as the starting material.

EXAMPLE 12-8
Preparation of Compound 1215

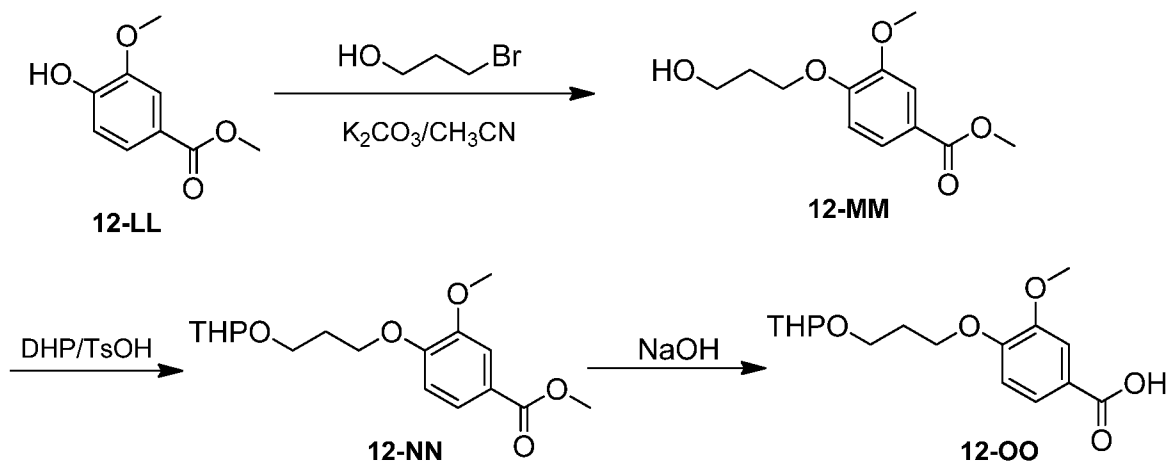


[0693] To a solution of **12-II** (2.6 g, 4.6 mmol) in anhydrous THF (30 mL) was added *t*-BuLi (18 mL, 1.3 M in THF) dropwise under nitrogen atmosphere at -78°C . The mixture was stirred at -78°C for 5 mins with TLC monitoring. The reaction was quenched by addition of aqueous NH_4Cl and extracted with EtOAc (3×100 mL). The organic layer was washed, dried and concentrated. The residue was purified on a silica gel column to give **12-JJ** (2.1 g) as a solid, which was used without further purification. +ESI-MS: m/z 572.2 $[\text{M} + \text{H}]^+$.

[0694] To a solution of **12-JJ** (2.1 g, 3.6 mmol) in DCM (25 mL) were added DMP (1.7 g, 4.0 mmol). The mixture was stirred at rt for 30 mins with TLC monitoring. The resulted solution was quenched by an aqueous NaHCO_3 solution and extracted with EtOAc. The combined organic layers were washed by saturated $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by pre-HPLC to give **12-KK** (600 mg) as a white solid. ^1H NMR: CD_3OD (400MHz): δ = 6.77 (d, $J=4.0$ Hz, 2 H), 6.34 (d, $J=8.4$ Hz, 2 H), 6.00-5.90 (m, 3 H), 5.68-5.64 (m, 1 H), 5.47 (d, $J=8.4$ Hz, 1 H), 4.25 (s, 2 H), 3.20 (s, 2 H), 2.33 (s, 6 H), 2.00-1.96 (m, 2 H), 1.71-1.75 (m, 2 H), 1.68 (s, 9 H). +ESI-MS: m/z 570.2 $[\text{M} + \text{H}]^+$.

[0695] To a solution of **12-KK** (300 mg, 0.53 mmol) in DCM (5 mL) was added TFA (5 mL) at 0°C. The solution was stirred at 40°C for 2 h with TLC monitoring. The reaction was quenched by the addition of a saturated NaHCO₃ solution, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by-HPLC to give compound **1215** (15 mg) as a white solid. +ESI-MS: m/z 440.1 [M + H]⁺.

EXAMPLE 12-9
Preparation of Compound 12-OO

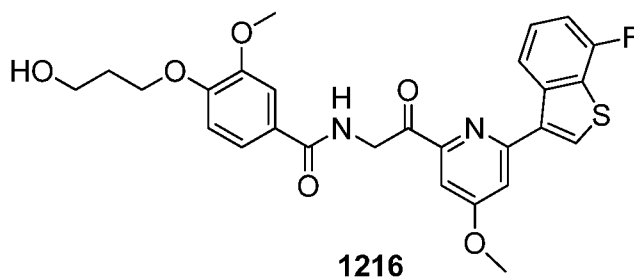


[0696] To a solution of **12-LL** (2.0 g, 11.0 mmol) in CH₃CN (10 mL) was added K₂CO₃ (4.55 g, 33.0 mmol) and 3-bromopropan-1-ol (4.55 g, 33.0 mmol). The mixture was heated to reflux for 12 h. The solution was evaporated and purified by column chromatography gel eluted with PE:EA=5:1 to give crude **12-MM** (2.1 g, 70.7%). ¹H-NMR (CDCl₃) δ = 7.62-7.64 (d, 1 H), 7.54-7.53 (d, 1 H), 6.90-6.88 (d, 1 H), 4.26-4.23 (m, 2 H), 3.90-3.89 (m, 8 H), 2.12-2.09 (m, 2 H).

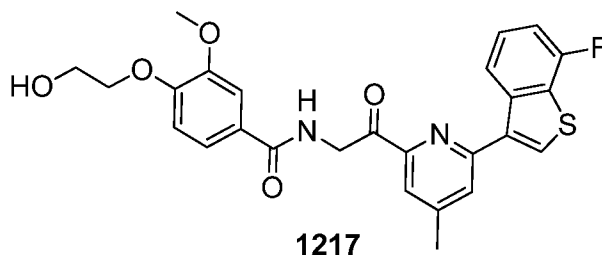
[0697] To a stirred solution of crude **12-MM** (2.1 g, 8.75 mmol) in DCM (10 mL) was added TsOH (1.3 g, 13.12 mmol) and DHP (2.2 g, 13.12 mmol). The mixture was stirred at rt for 12 h. The solution was quenched with an aqueous NaHCO₃ solution, and the organic layer was combined and purified by column chromatography gel eluted with PE:EA=5:1 as elute to give **12-NN** (1.6 g, 50.0%).

[0698] To a solution of **12-NN** (1.6 g, 5.9 mmol) in THF (20 mL) was carefully added 2 N NaOH solution (9 mL, 18 mmol) and stirred at rt for 3 h. The solution was evaporated and dissolved with DCM. The solution was acidified to pH=7 with 1N HCl

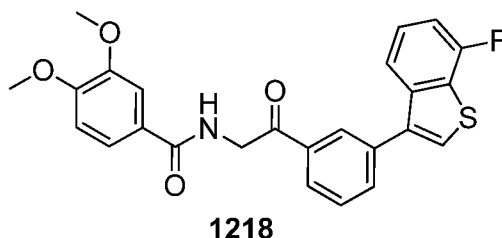
solution, and the aqueous layer was extracted with DCM. The organic layer was combined and purified by column chromatography gel eluted with PE:EA=3:1 as elute to give **12-00** (1.0 g, 65.4%).



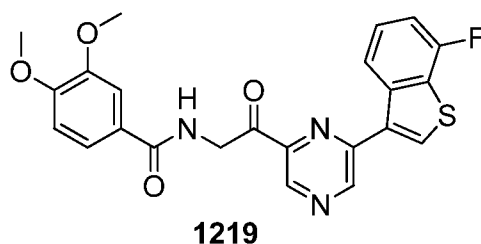
[0699] Compound **1216** was obtained following the procedure for obtaining compound **1200** by using **12-00** and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)-4-methoxypyridin-2-yl) ethanol as the starting materials. Compound **1216** was obtained as a white solid. +ESI-MS: m/z 525.1 $[M + H]^+$.



[0700] Compound **1217** was obtained following the procedure for obtaining compound **1200** by using 3-methoxy-4-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)benzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)-4-methylpyridin-2-yl)ethanol as the starting materials. Compound **1217** was obtained as a white solid. +ESI-MS: m/z 495.1 $[M + H]^+$.



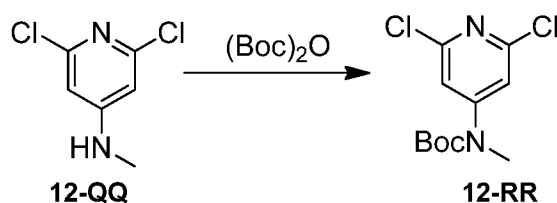
[0701] Compound **1218** was obtained following the procedure for obtaining compound **1200** by using 1,3-dibromobenzene as the starting material. Compound **1218** was obtained as a white solid. +ESI-MS: m/z 450.0 $[M + H]^+$.



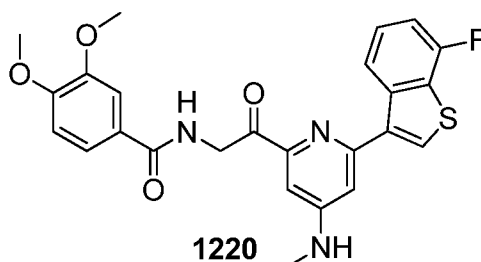
[0702] Compound **1219** was obtained following the procedure for obtaining compound **1200** by using 2,6-dichloropyrazine as the starting material. Compound **1219** was obtained as a white solid (100 mg, 75%). +ESI-MS: m/z 452.1 $[M + H]^+$.

EXAMPLE 12-10

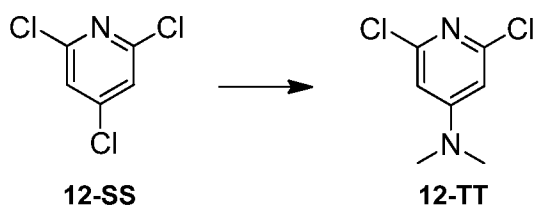
Preparation of Compound 12-RR



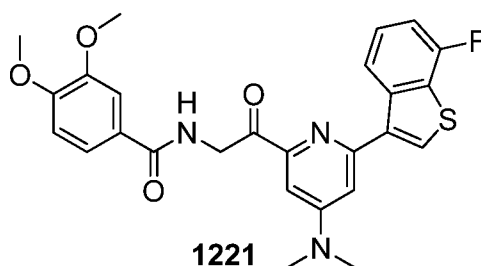
[0703] To a solution of **12-QQ** (1.77 g, 10.0 mmol) in DCM (60 mL) was added Et_3N (2.02 g, 20.0 mmol) and $(\text{Boc})_2\text{O}$ (2.18 g, 10.0 mmol). The mixture was stirred at rt overnight. The mixture was neutralized with a saturated NaHCO_3 solution. The organic layer was evaporated to give the crude product. The residue was purified by a silica gel column using PE/EA = 20/1 to 5/1 as elute to afford **12-RR** as a white solid (2.5 g, 90.3 %). +ESI-MS: m/z 277.0 $[M + H]^+$.



[0704] Compound **1220** was obtained following the procedure for obtaining compound **1200** by using **12-RR** as the starting material. +ESI-MS; m/z 480.1 $[M + H]^+$.

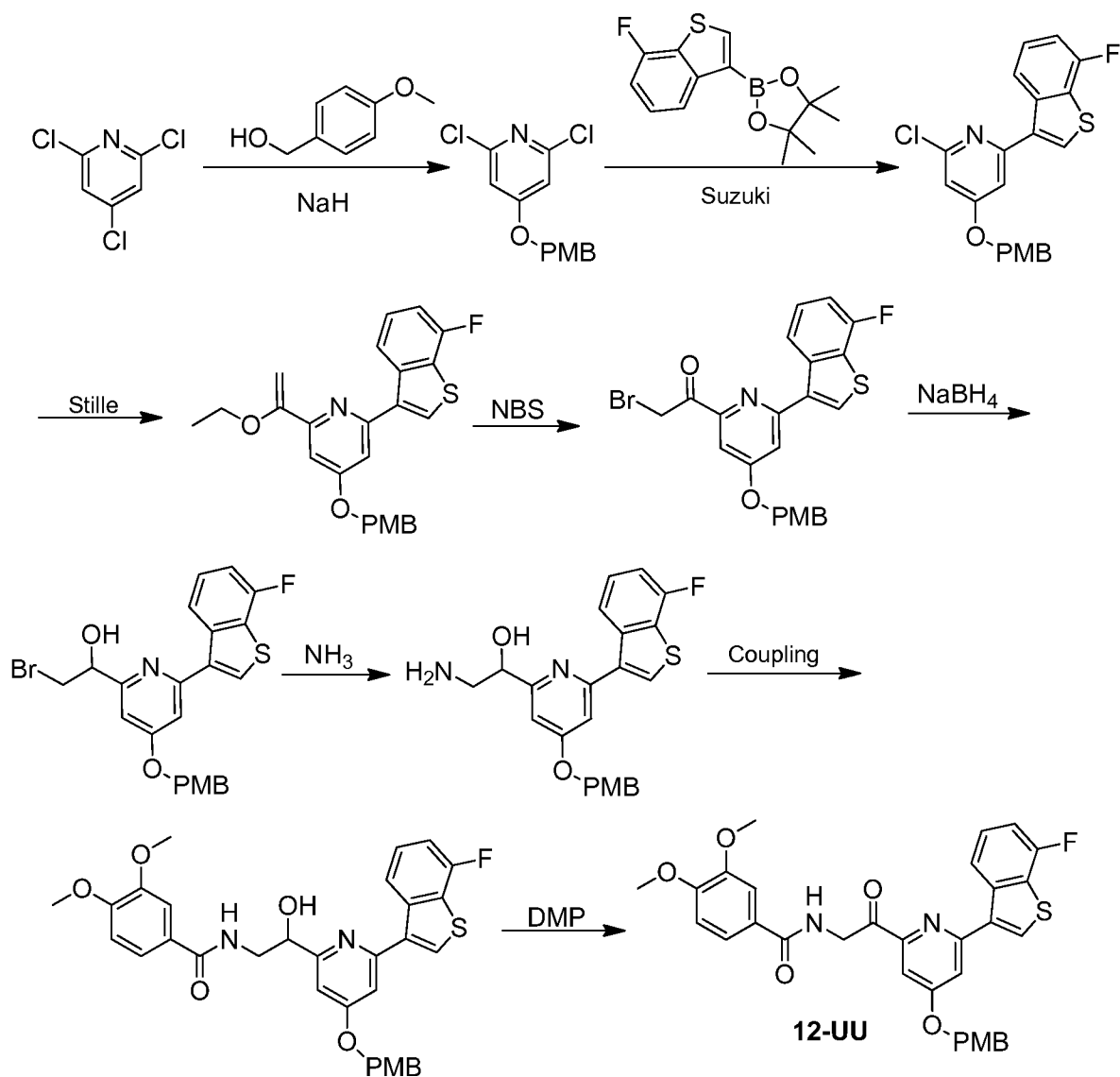
EXAMPLE 12-11**Preparation of Compound 12-TT**

[0705] A mixture of **12-SS** (10.0 g, 55.6 mmol), dimethylamine hydrochloride (4.5 g, 55.6 mmol) and Et₃N (8.0 g, 55.6 mmol) in DMF (80 mL) in a sealed tube was heated to 80°C for 8 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **12-TT** (4.0 g) as a white solid. ¹H-NMR: DMSO (400MHz): δ = 6.66 (s, 2 H), 2.99 (s, 6 H).

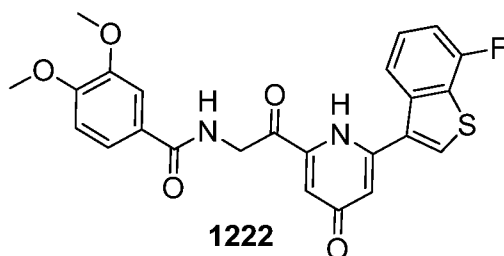


[0706] Compound **1221** was obtained following the procedure for obtaining compound **1200** by using **12-TT** as the starting material. Compound **1221** was obtained as a white solid +ESI-LCMS: m/z = 494.0 [M + H]⁺.

EXAMPLE 12-12
Preparation of Compound 12-UU

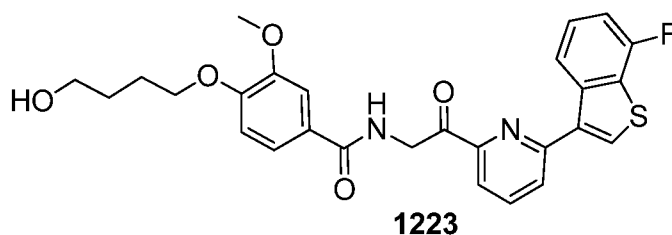


[0707] Compound **12-UU** was obtained following the procedure for obtaining compound **1200** by using 2,4,6-trichloropyridine as the starting material.



[0708] To a solution of **12-UU** (90 mg, 0.15 mmol) in DCM/H₂O (1.5 mL, DCM/H₂O=10:1) was added DDQ (69 mg, 0.3 mmol). The mixture was stirred at 30°C for 3

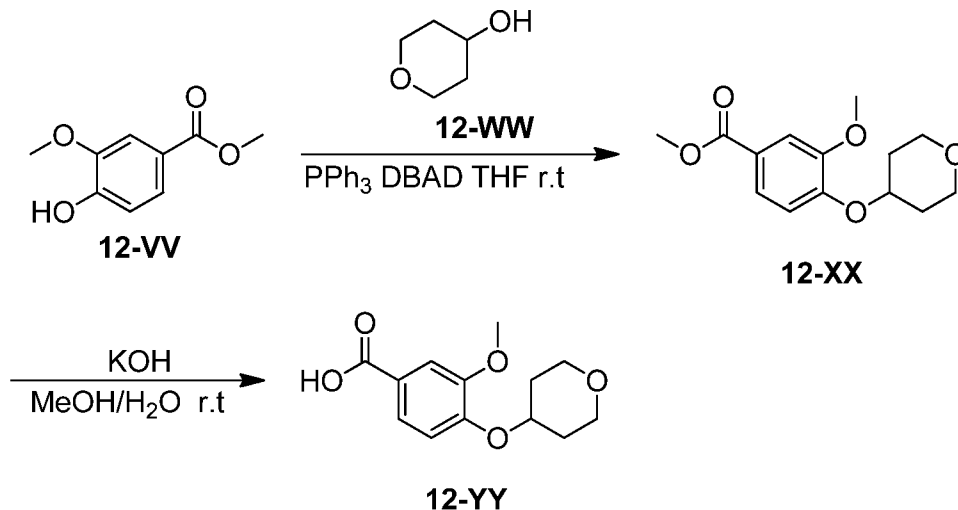
h. The mixture was neutralized with a saturated NaHCO_3 solution. The mixture was extracted with DCM (300 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column on silica gel using DCM:MeOH=50:1 to 30:1 as elute to give compound **1222** (30 mg, 43%). +ESI-MS: m/z 466.9 $[\text{M} + \text{H}]^+$.



[0709] Compound **1223** was obtained following the procedure for obtaining compound **1200** by using 3-methoxy-4-(4-((2-(trimethylsilyl)ethoxy)methoxy)butoxy)benzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)ethanol as the starting materials. Compound **1223** was obtained as a white solid +ESI-MS: m/z 509.0 $[\text{M} + \text{H}]^+$.

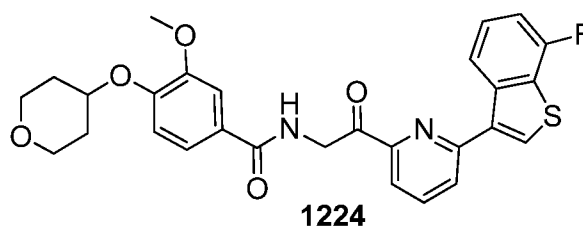
EXAMPLE 12-13

Preparation of Compound 12-YY

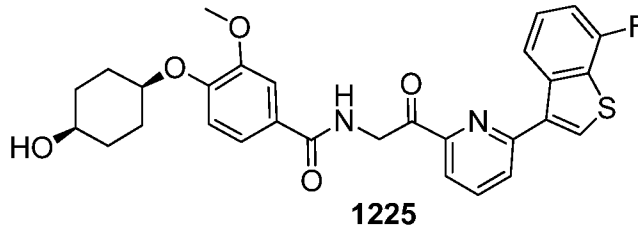


[0710] To a stirred solution of **12-VV** (1.09 g, 6 mmol) in THF (10 mL) was added **12-WW** (0.612 g, 6 mmol), PPh_3 (1.886 g, 7.2 mmol) and DBAD (1.555 g, 7.2 mmol). The mixture was refluxed for 48 h. The solution was evaporated to give the crude product. The residue was purified by column chromatography gel using PE:acetone=8:1 as the elute to give **12-XX** (900 mg, 52.9 %).

[0711] To a solution of crude **12-XX** (800 mg, 3.38 mmol) in MeOH (15 mL) was added a solution of 1N KOH (757 mg, 13.53 mmol). The mixture was stirred at rt for 1 h. After complete conversion, as indicated by TLC (PE:EA=2:1), the solvent was washed with water and extracted with EtOAc. The aqueous phase was acidified to pH=3 with 1N citric acid solution. The solution was extracted with EtOAc, and the organic phase was concentrated to give crude **12-YY**. After purification, **12-YY** (660 mg, yield: 87.2%) was obtained.



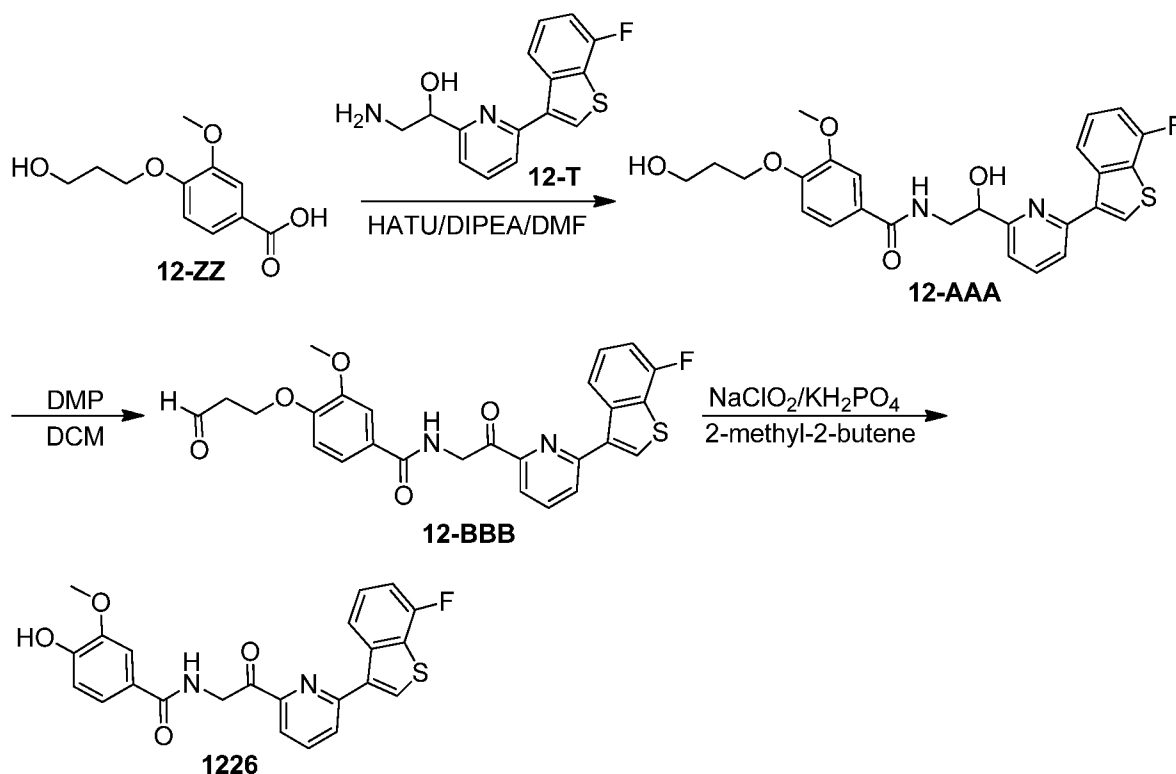
[0712] Compound **1224** was obtained following the procedure for obtaining compound **1200** by using 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)ethanol and **12-YY** as the starting materials. Compound **1224** was obtained as a white solid +ESI-MS: m/z 521.1 $[M + H]^+$.



[0713] Compound **1225** was obtained following the procedure for obtaining compound **1200** by using 3-methoxy-4-(((1s,4s)-4-((2-(trimethylsilyl)ethoxy)methoxy)cyclohexyl)oxy)benzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)ethanol as the starting materials. Compound **1225** was obtained as a white solid +ESI-MS: m/z 535.1 $[M + H]^+$.

EXAMPLE 12-14

Preparation of Compound 1226

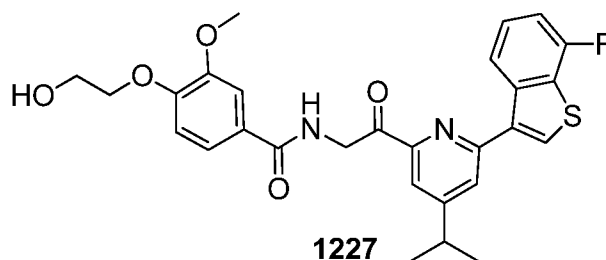


[0714] To a solution of **12-ZZ** (100 mg, 0.442 mmol), HATU (251 mg, 0.66 mmol) and DIPEA (170 mg, 1.32 mmol) in anhydrous DMF (2 mL) was added **12-T** (127 mg 0.442 mmol) at 25°C. The solution was stirred for 10 h at rt and then diluted with 1.0 N aqueous NaHCO₃ solution (40 mL x 2), extracted with EA (20 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified on a silica gel column to give **12-AAA** (120 mg, 54.8%). +ESI-MS: m/z 497.1 [M+H]⁺.

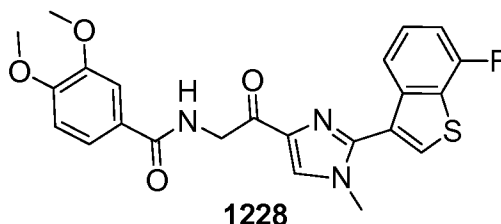
[0715] To a mixture of **12-AAA** (120 mg, 0.24 mmol) in DCM (10 mL) was added DMP (410 mg, 0.96 mmol). The mixture was stirred at rt for 30 mins with TLC monitoring. The solution was quenched with aqueous NaHCO₃ solution and extracted with EtOAc. The combined organic layers were washed with saturated Na₂S₂O₃ and brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC to give **12-BBB** (100 mg, 84.7%). +ESI-MS: m/z 493.1[M +H]⁺.

[0716] To a solution of **12-BBB** (100 mg, 0.2 mmol) in acetone: H₂O (1 mL/1 mL) were added KH₂PO₄ (23 mg, 0.22 mmol), NaClO₂ (36 mg, 0.4 mmol) and 2-methyl-2-

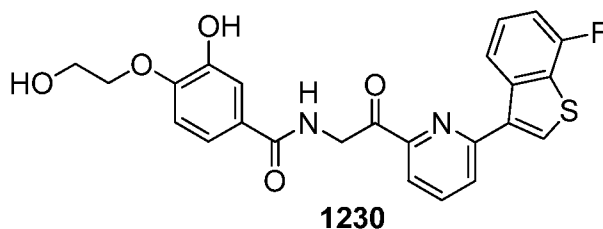
butene (116 mg, 2 mmol) at 0°C. The mixture was stirred for 30 mins. The resulted solution was quenched with a Na₂S₂O₃ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC(FA) to give compound **1226** (20 mg, 17.2%). +ESI-MS: m/z 436.9 [M + H]⁺.



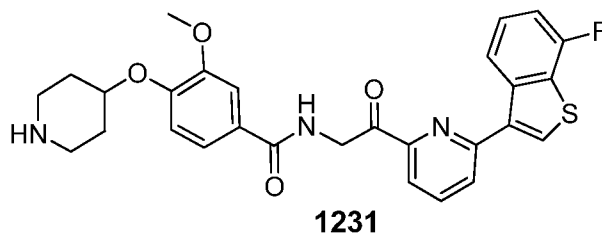
[0717] Compound **1227** was obtained following the procedure for obtaining compound **1200** by using 2,4,6-trichloropyridine as the starting material. Compound **1227** was obtained as a white solid +ESI-MS: m/z 523.0 [M + H]⁺.



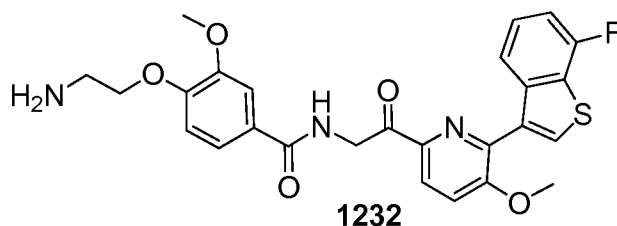
[0718] To a mixture of compound **1215** (44 mg, 0.1 mmol) in DMF (4 mL) was added K₂CO₃ (27 mg, 0.2 mmol). The solution was heated to 60°C and MeI (5.6 g, 20 mmol) was added. The solution was stirred for 2 h at 60°C. The water was added and extracted with EtOAc. The organic phase was concentrated to give the crude product. Further purification by prep-HPLC gave compound **1228** as a colorless solid (6 mg, 14 %). +ESI-MS: m/z 454.0 [M + H]⁺.



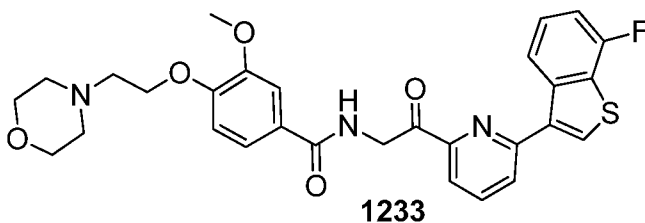
[0719] Compound **1230** was obtained following the procedure for obtaining compound **1200** by using 2,6-dichloropyridine as the starting material. Compound **1230** was obtained as a white solid. +ESI-MS: m/z 467.1 $[M+H]^+$.



[0720] Compound **1231** was obtained following the procedure for obtaining compound **1200** by using 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-3-methoxybenzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)ethanol as the starting materials. Compound **1231** was obtained as a yellow solid (50 mg, 50 %). +ESI-MS: m/z 519.9 $[M+H]^+$.

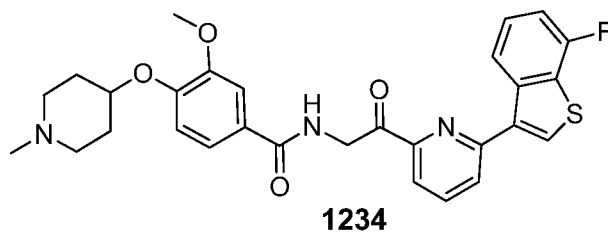


[0721] Compound **1232** was obtained following the procedure for obtaining compound **1200** by using 4-(2-((tert-butoxycarbonyl)amino)ethoxy)-3-methoxybenzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)-5-methoxypyridin-2-yl)ethanol as the starting materials. Compound **1232** was obtained as a white solid. +ESI-MS: m/z 510.1 $[M+H]^+$.



[0722] Compound **1233** was obtained following the procedure for obtaining compound **1200** by using 4-(2-((tert-butoxycarbonyl)amino)ethoxy)-3-methoxybenzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)-5-methoxypyridin-2-yl)ethanol as the

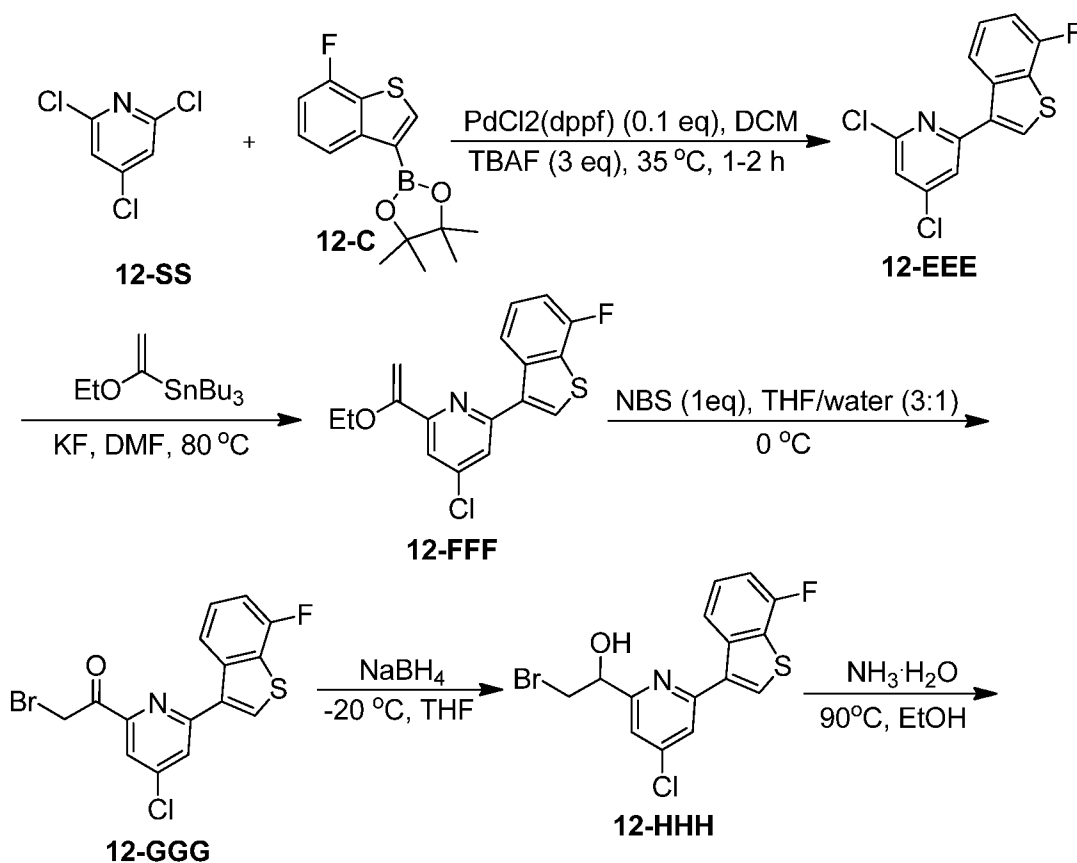
starting materials. Compound **1233** was obtained as a white solid. +ESI-MS: m/z 549.9 $[M + H]^+$.

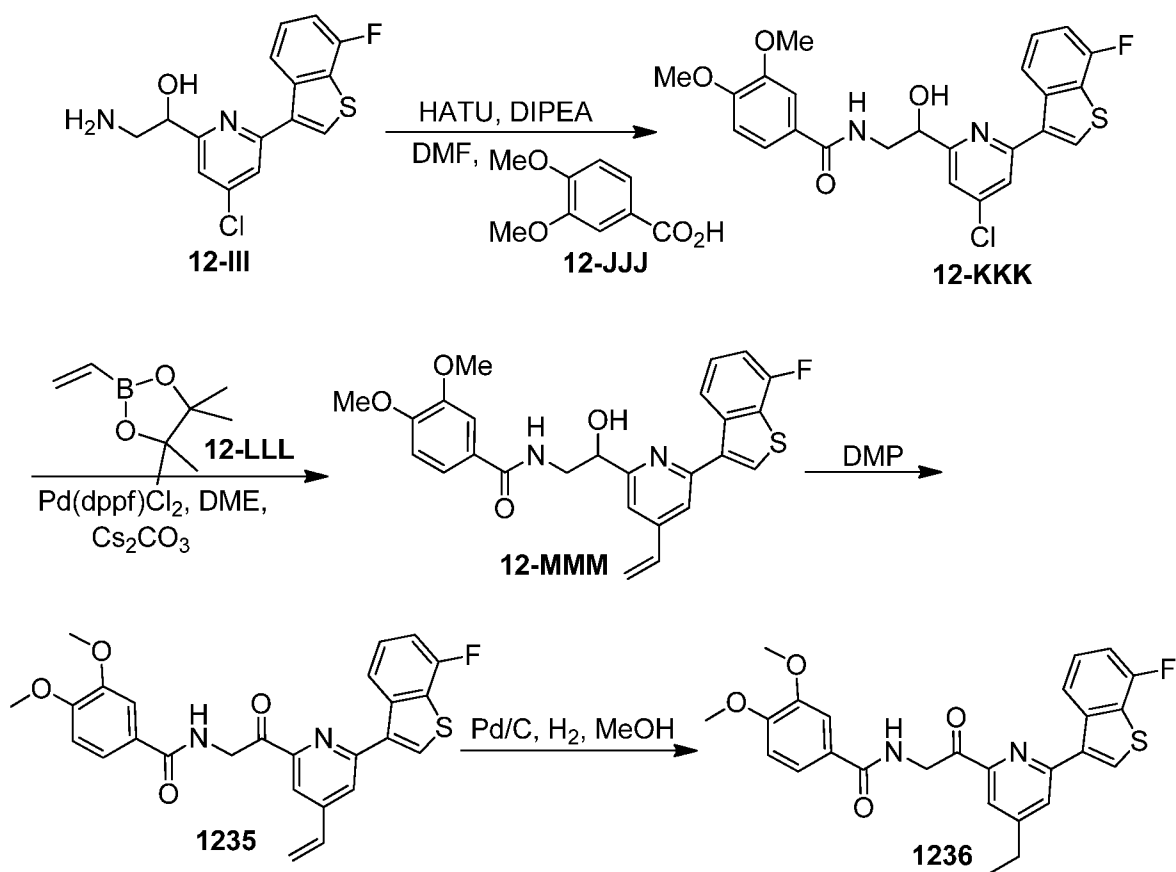


[0723] Compound **1234** was obtained following the procedure for obtaining compound **1200** by using 3-methoxy-4-((1-methylpiperidin-4-yl)oxy)benzoic acid and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)-5-methoxypyridin-2-yl)ethanol as the starting materials. Compound **1234** was obtained as a white solid. +ESI-MS: m/z 534.1 $[M + H]^+$.

EXAMPLE 12-15

Preparation of Compound 1236





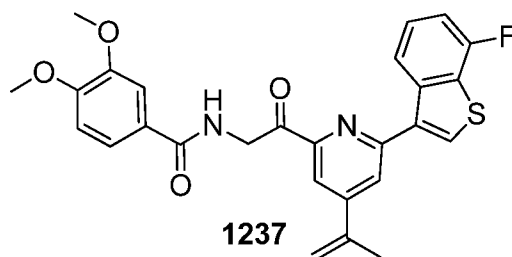
[0724] To a solution of **12-SS** (18.2 g, 0.1 mol) in DCM (200 mL) was added **12-C** (27.8 g, 0.1 mol), TBAF (78 g, 0.3 mol) and Pd(dppf)Cl_2 (7.31 g, 0.01 mol). The mixture was stirred at 30-40°C for 2 h and monitored by TLC. The reaction solution was filtered and the filtrates were washed with brine. The organic layer was concentrated by rotary evaporator, and the product was purified by silica column chromatography (9 g, 30%). +ESI-MS: m/z 298.0 $[\text{M} + \text{H}]^+$.

[0725] Compound **12-EEE** to **12-KKK** were obtained following the procedure for obtaining Compound **1200** by using **12-EEE** as the starting material.

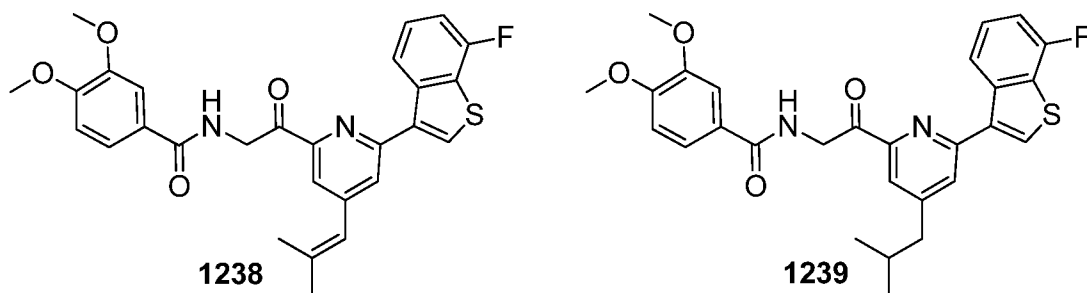
[0726] To a solution of **12-KKK** (972 mg, 2 mmol) in DME (15 mL) was added **12-LLL** (616 mg, 4 mmol), Pd(dppf)Cl_2 (146 mg, 0.2 mmol) and Cs_2CO_3 (1.3 g, 4 mmol). The mixture was stirred for 16 h at 120°C under N_2 . The reaction solution was filtered and to give a clear solution. The solution was extracted with EtOAc (80 mL) and washed with brine (20 mL x 3). Compound **12-MMM** was purification by silica column chromatography using EA:PE = 1:1 as the elute (900 mg, 94%). ESI-MS: m/z 478.9 $[\text{M} + \text{H}]^+$.

[0727] To a solution of **12-MMM** (478 mg, 1 mmol) in DCM (10 mL) was added DMP (848 mg, 2 mmol) at 0°C. The reaction was allowed to proceed for 3 h. The mixture was washed with brine (5 mL x 3), and the organic layer was dried and concentrated to give the crude product. The product was purified by silica column chromatography using PE:EA = 2:1 as the elute to give the compound **1235** (220 mg, 46%). +ESI-MS: m/z 476.8 $[M+H]^+$

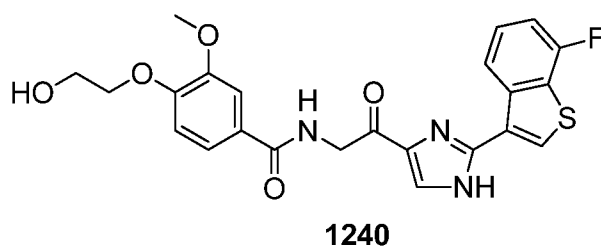
[0728] A mixture of compound **1235** (119 mg, 0.25 mmol) and Pd/C (50 mg) in MeOH (10 mL) was hydrogenated under H₂ (1 atm) for 1 h at rt. The suspension was filtered through a pad of Celite, and the filter cake was washed with MeOH (10 mL x 3). The combined filtrates were concentrated to give the product. Compound **1236** was purified by prep-HPLC to give the product (15 mg, 12 %). +ESI-MS: m/z 479.0 $[M+H]^+$.



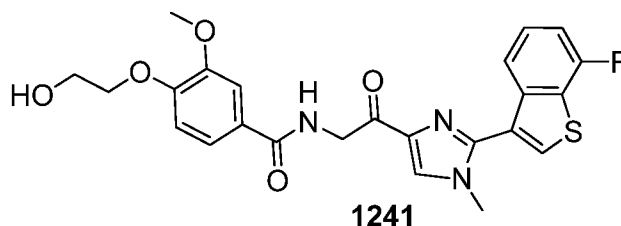
[0729] Compound **1237** was obtained following the procedure for obtaining compound **1235** by using 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane and **12-KKK** as the starting materials. Compound **1237** was obtained as a white solid. +ESI-MS: m/z 490.9 $[M+H]^+$.



[0730] Compounds **1238** and **1239** were obtained following the procedure for obtaining compound **1235** by using **12-KKK** and 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane as the starting materials. Compounds **1238** and **1239** were each obtained as a white solid. Compound **1238**: +ESI-MS: m/z 504.9 $[M+H]^+$. Compound **1239**: +ESI-MS: m/z 506.8 $[M+H]^+$.

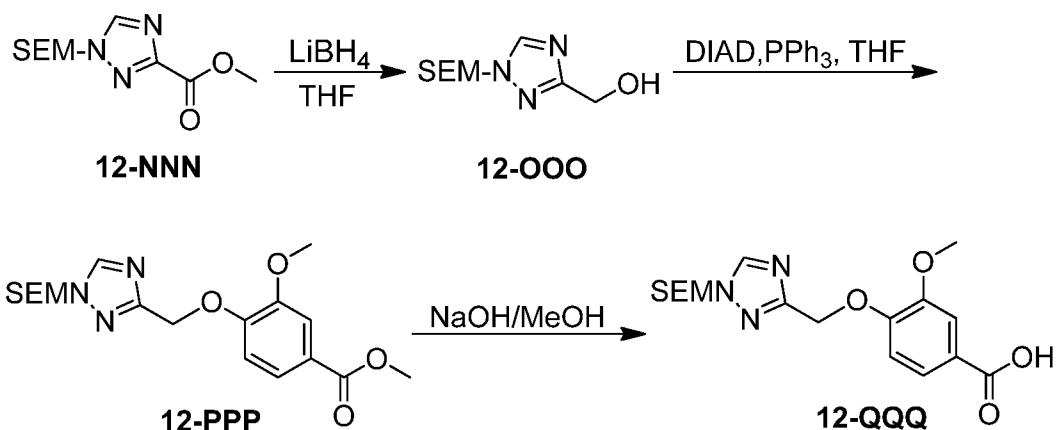


[0731] Compound **1240** was obtained following the procedure for obtaining compound **1215** by using 2,4,5-tribromo-1H-imidazole as the starting material. Compound **1240** was obtained as a white solid. +ESI-MS: m/z 469.8 [M + H]⁺.



[0732] To a mixture of compound **1240** (100 mg, 0.2 mmol) in DMF (4 mL), K₂CO₃ (27 mg, 0.2 mmol) was added. The solution was heated to 60°C and MeI (5.6 g, 20 mmol) was added. The solution was stirred for 2 h at 60°C. The water was added, and the solution was extracted with EtOAc. The organic phase was concentrated to give the crude product. Further purification by prep-HPLC gave compound **1241** as a colorless solid (50 mg, 48 %). +ESI-MS: m/z 483.9 [M + H]⁺.

EXAMPLE 12-16
Preparation of Compound 12-QQQ

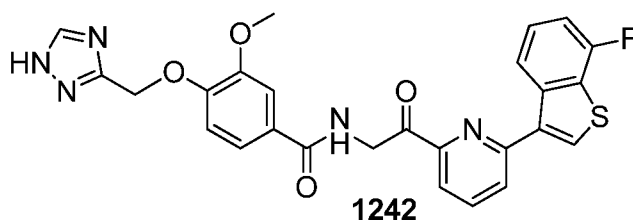


[0733] To a solution of **12-NNN** (5g, 19.4 mmol) in THF (30 mL) was added LiBH₄ (1.7 g, 77.8 mmol) at rt. The solution was heated to reflux and stirred for 2 h. The

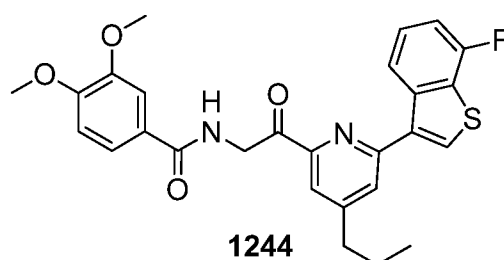
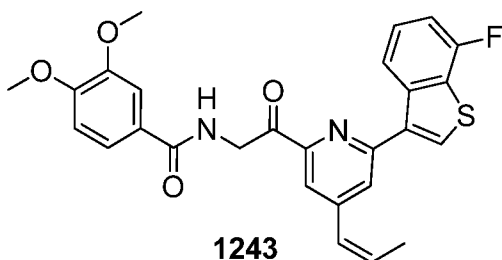
solution was quenched with H₂O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give **12-000** (1.3 g, 73%).

[0734] To a solution of **12-000** (3.3 g, 14.4 mmol) and methyl 4-hydroxy-3-methoxybenzoate (2.62 g, 14.4 mmol) in THF (20 mL) were added DIAD (3.49 g, 17.3 mmol) and PPh₃ (4.5 g, 17.3 mmol). The solution was heated to reflux and stirred for 15 h. The solution was washed with brine and extracted with EtOAc. The organic phase was concentrated, and the residue was used in the next step without further purification.

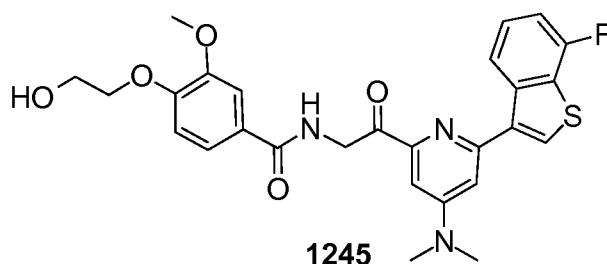
[0735] To a solution of **12-PPP** (4 g crude, 10 mmol) in methanol (20 mL), was added NaOH aqueous (20 mL, 1M). The mixture was stirred for 4 h at 60°C. The solution was cooled to rt, acidified using 1N HCl and extracted with EtOAc. The organic phase was dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to provide **12-QQQ** (400 mg, 50%).



[0736] Compound **1242** was obtained following the procedure for obtaining compound **1215** by using 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)ethanol and **12-QQQ** as the starting materials. Compound **1242** was obtained as a white solid. +ESI-MS: m/z 517.8 [M+H]⁺.

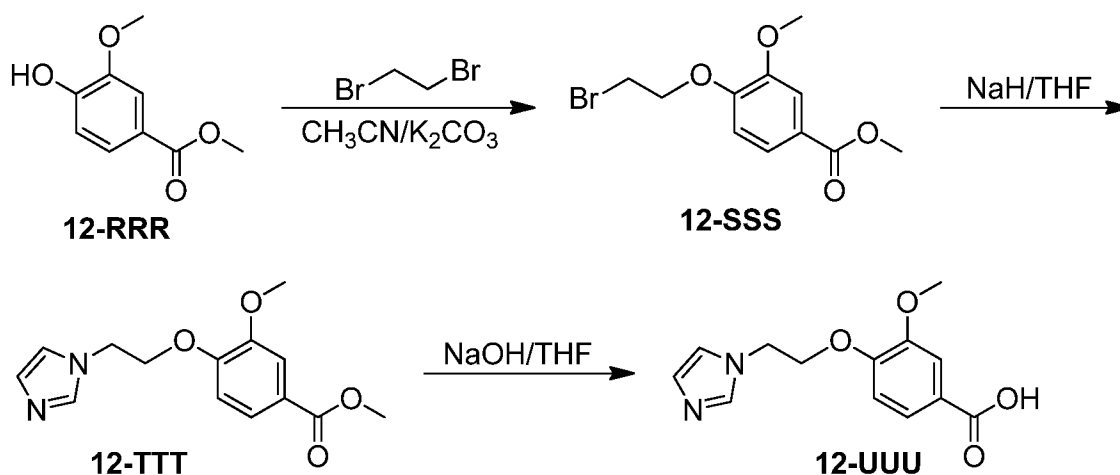


[0737] Compounds **1243** and **1244** were obtained following the procedure for obtaining compound **1235** by using **12-KKK** and 4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane as the starting materials. Compounds **1243** and **1244** were each obtained as a white solid. Compound **1243**: +ESI-MS: m/z 491.1 [M+H]⁺. Compound **1244**: +ESI-MS: m/z 593.1 [M+H]⁺.



[0738] Compound **1245** was obtained following the procedure for obtaining compound **1221** by using 2,4,6-trichloropyridine as the starting material. Compound **1245** was each obtained as a white solid. +ESI-MS: m/z 524.1 $[M+H]^+$.

EXAMPLE 12-17
Preparation of Compound 12-UUU

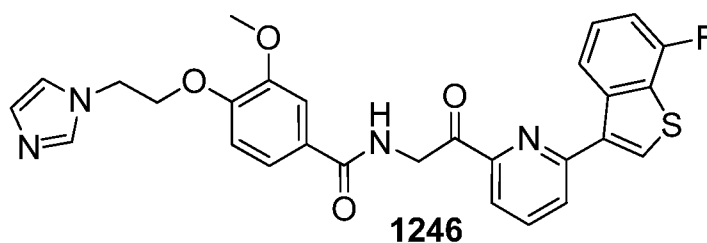


[0739] To a solution of **12-RRR** (3.6 g, 20 mmol), 1,2-dibromoethane (7.4 g, 40 mmol) in CH_3CN (30 mL) were added K_2CO_3 (4.5 g, 22.2 mmol). The solution was heated to reflux and stirred for 15 h. The solution was washed with brine and extracted with EtOAc. The organic phase was concentrated, and the residue was directly used in the next step.

[0740] To a solution of imidazole (680 mg, 10.0 mmol) in THF (30 mL) were added NaH (480 mg, 22.2 mmol, 60% in mineral oil). The mixture was stirring at rt for 0.5 h, and **12-SSS** (2.88 g, 10 mmol) in THF (10 mL) was added dropwise. The solution was stirred for 15 h at rt. The solution was washed with brine and extracted with EtOAc. The organic phase was concentrated, and the residue was directly used in the next step. +ESI-MS: m/z 277.1 $[M+H]^+$.

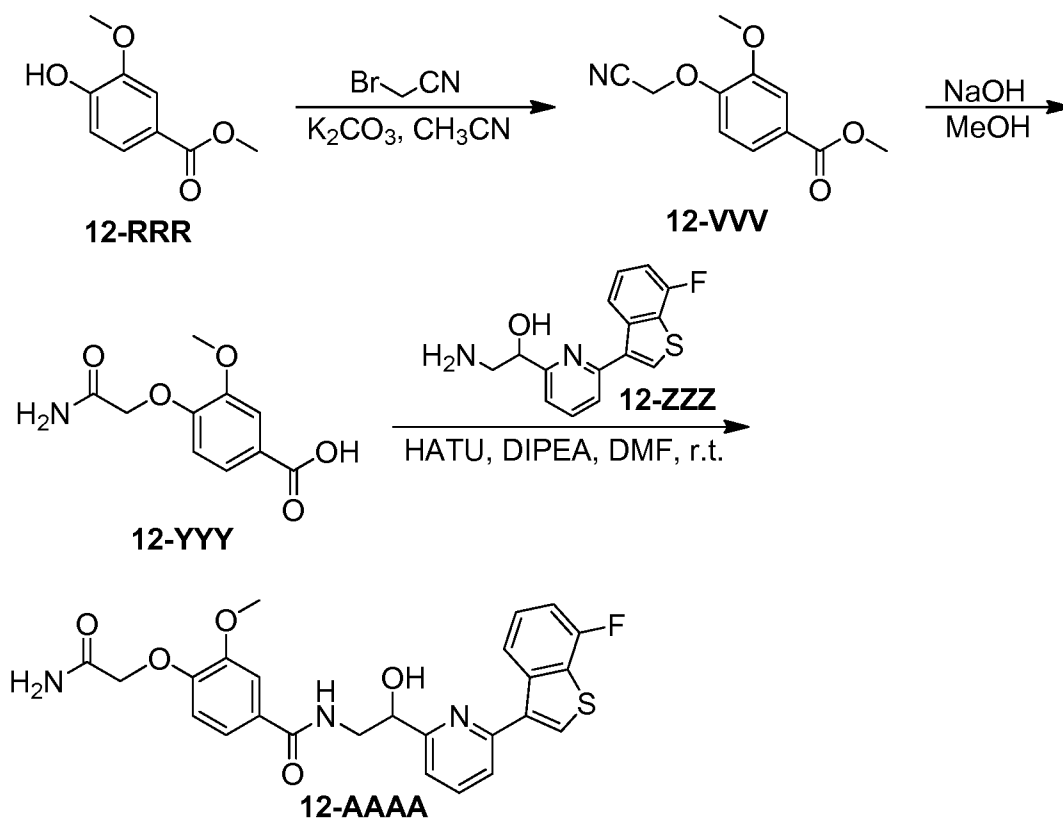
[0741] To a solution of **12-TTT** (2.76 g crude, 10 mmol) in methanol (20 mL) was added NaOH aqueous (20 mL, 1M). The mixture was stirred for 4 h at 60°C. The

solution was cooled to rt, acidified to pH=3 using 1N HCl solution and extracted with EtOAc. The organic phase was dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to provide **12-UUU** (1.4 g, 50%).



[0742] Compound **1246** was obtained following the procedure for obtaining compound **1215** by using 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)ethanol and **12-UUU** as the starting materials. Compound **1246** was each obtained as a white solid. +ESI-MS: m/z 531.0 [M + H]⁺.

EXAMPLE 12-18
Preparation of Compound 12-AAAA

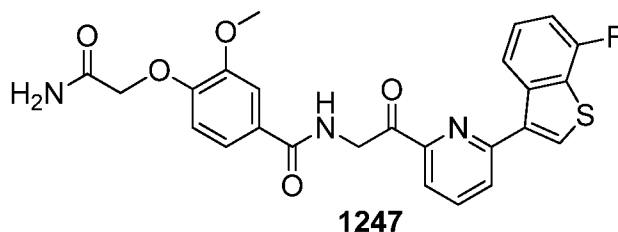


[0743] To a solution of **12-RRR** (1.82 g, 10 mmol) and K₂CO₃ (2.76 g, 20 mmol) in CH₃CN (20 mL) at rt was slowly added 2-bromoacetonitrile (2.4 g, 20 mmol). The

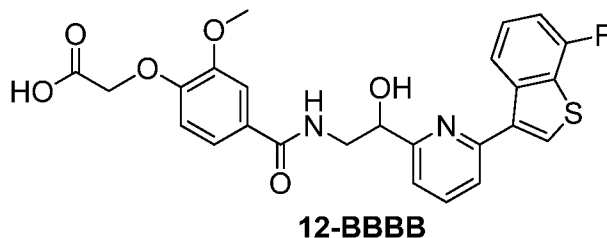
mixture was heated to reflux and stirred for 15 h. The solvent were removed under reduced pressure. Purification by column chromatography on silica gel (PE:EA=3:1) provided **12-VVV** (2 g, 90%).

[0744] To a solution of **12-VVV** (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 rt, acidified to pH=4 using 1N HCl solution and extracted with EtOAc. The organic phase was dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to provide **12-YYY** (1.1 g, 50%).

[0745] To a solution of **12-YYY** (226 mg, 0.1 mmol) in DMF (3 mL) were added HATU (570 mg, 1.5 mmol) and DIPEA (387 mg, 3 mmol) at rt. The solution was stirred for 10 min at rt. Compound **12-ZZZ** (287 mg, 1 mmol) was added and stirred for 1 h. The solution was extracted with EtOAc and washed with H₂O. The organic phase was concentrated and purified by prep-TLC to give **12-AAAA** (200 mg, 40%). +ESI-MS: m/z 495.9 [M + H]⁺.

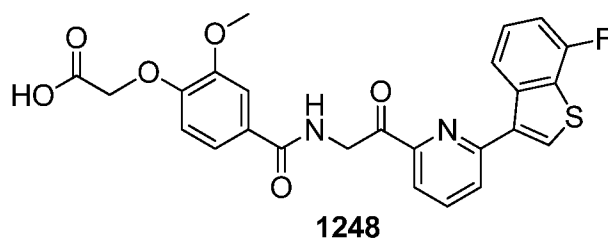


[0746] A solution of **12-AAAA** (50 mg, 0.1 mmol) in DMSO (1 mL) was added IBX (56 mg, 0.2 mmol) at 30°C, and the mixture was stirred for 2 h. The solution was purified by prep-HPLC (FA) to provide compound **1247** as a white solid (20 mg, 40 %). +ESI-MS: m/z 493.9 [M + H]⁺.

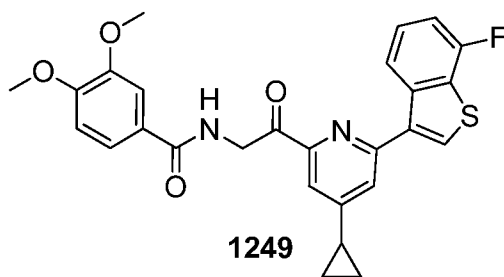


[0747] To a solution of compound **1247** (495 mg, 1.0 mmol) in MeOH (10 mL) was added aqueous NaOH (10 mL, 1M). The mixture was stirred for 4 h at 60°C. The solution was cooled to rt, acidified to pH=3 using 1N HCl solution and extracted with

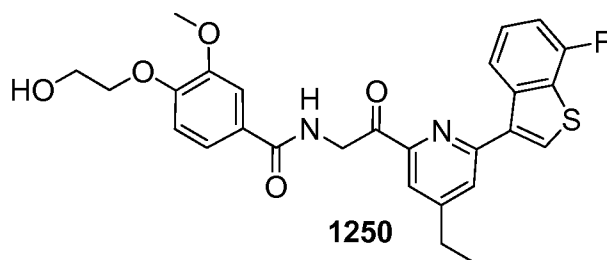
EtOAc. The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **12-BBBB** (490 mg, 99 %). +ESI-MS: m/z 497.1 $[\text{M} + \text{H}]^+$.



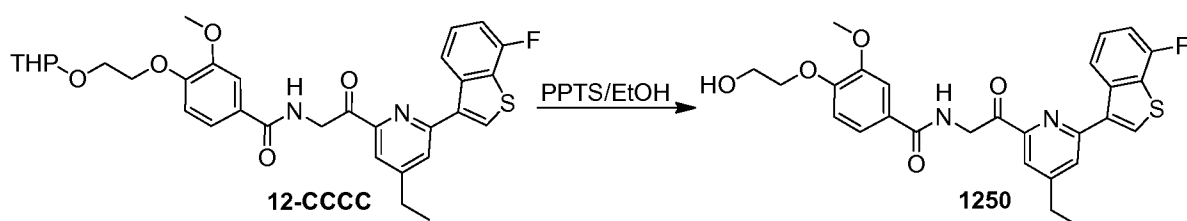
[0748] To a solution of **12-BBBB** (50 mg, 0.1 mmol) in DMSO (1 mL) was added IBX (56 mg, 0.2 mmol) at 30°C and stirred for 2 h. The solution was purified by prep-HPLC (FA) to provide compound **1248** as a white solid (20 mg, 40%). +ESI-MS: m/z 494.7 $[\text{M} + \text{H}]^+$.



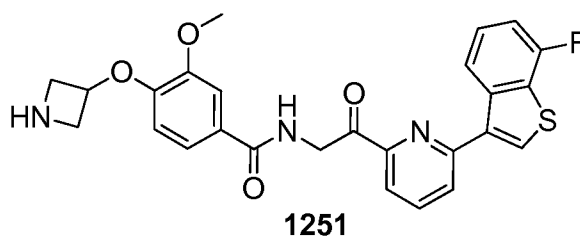
[0749] Compound **1249** was obtained following the procedure for obtaining compound **1235** by using N-(2-(4-chloro-6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)-2-hydroxyethyl)-3,4-dimethoxybenzamide and 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1249** was each obtained as a white solid. +ESI-MS: m/z 491.0 $[\text{M} + \text{H}]^+$.



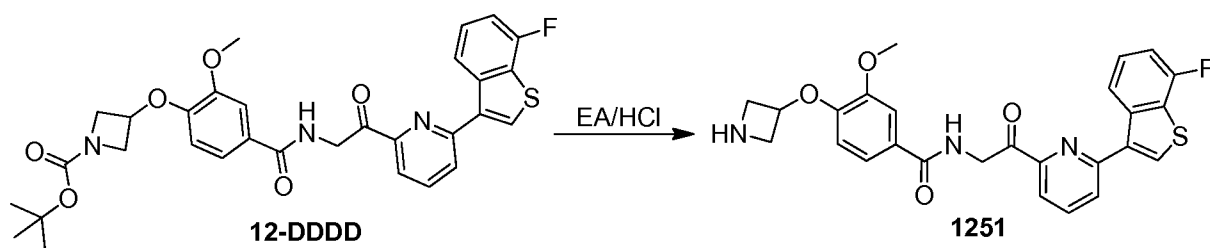
[0750] Compound **1250** was obtained following the procedure for obtaining compound **1235** by using N-(2-(4-chloro-6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)-2-hydroxyethyl)-3-methoxy-4-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)benzamide and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane as the starting materials.



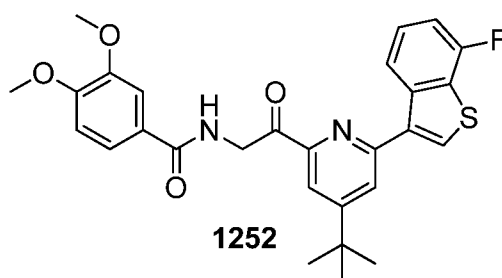
[0751] To a solution of **12-CCCC** (160 mg, 0.27 mmol) in EtOH (5 mL) was added PPTS (6.8 mg, 0.027 mmol), and stirred at 70°C for 2 h. The mixture was diluted with water and extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give the crude product, which was purified by prep-HPLC to give compound **1250** (50mg) as a white solid. +ESI-MS: m/z 509.1 [M+H]⁺.



[0752] Compound **1251** was obtained following the procedure for obtaining compound **1242** by using tert-butyl 3-hydroxyazetidine-1-carboxylate as the starting material.

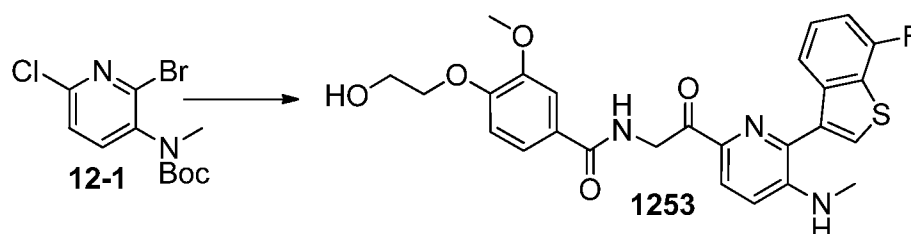


[0753] To a solution of **12-DDDD** (150 mg, 0.25 mmol) in EA (2 mL) was added HCl/EA (2 mL) at 0°C and stirred for 0.5 h. The solvent was removed by bubbling with N₂. The residue was purified by prep-HPLC to provide compound **1251** as a white solid (20 mg, 16.3 %). +ESI-MS: m/z 491.8 [M + H]⁺.



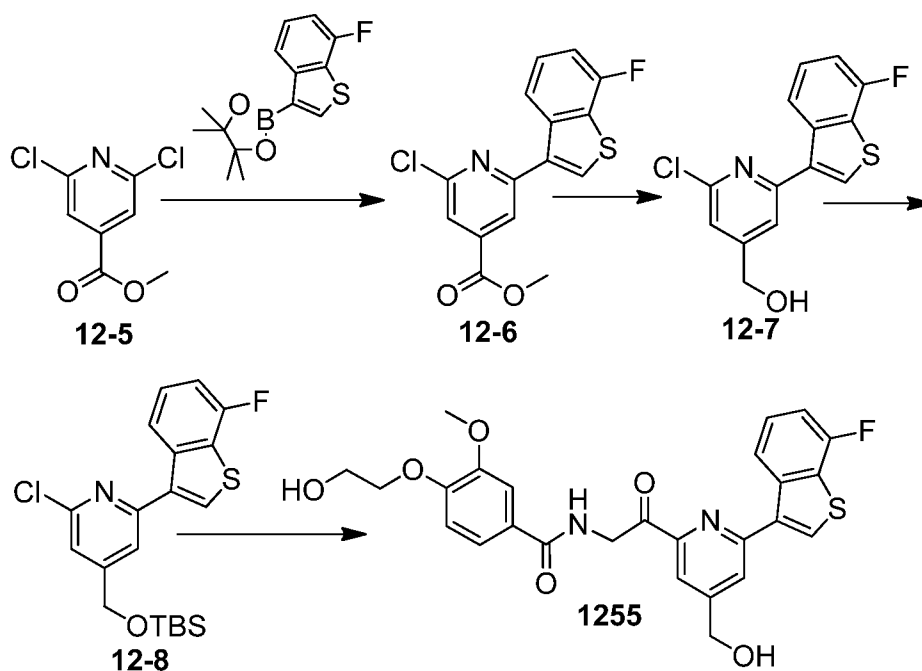
[0754] Compound **1252** was obtained following the procedure for obtaining compound **1200** by using 4-(tert-butyl)-2,6-dichloropyridine as the starting material. Compound **1252** was obtained as a white solid. +ESI-MS: m/z 507.0 $[M+H]^+$.

EXAMPLE 12-19
Preparation of Compound 1253



[0755] Compound **1253** was obtained following the procedure for obtaining compound **1200** by using **12-1** as the starting material. Compound **1253** was obtained as a white solid. +ESI-MS: m/z : 509.9 $[M+H]^+$.

EXAMPLE 12-20
Preparation of Compound 1255



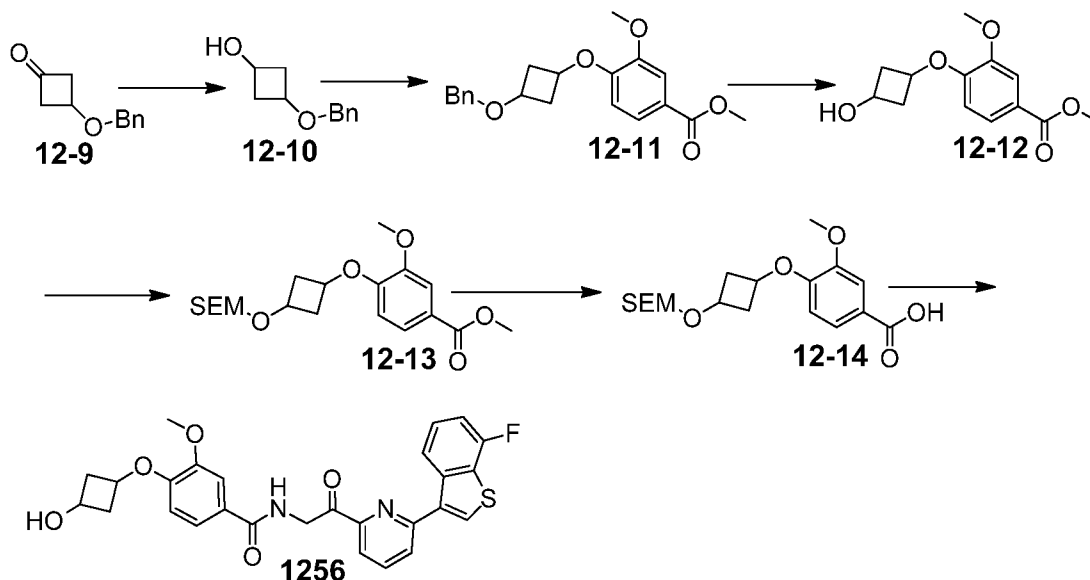
[0756] To a mixture of **12-5** (4 g, 19.3 mmol) and the dioxaborolane (5.38 mg, 19.3 mmol) in dioxane/H₂O (10 mL/2 mL) were added Pd(dppf)Cl₂ (1.41 g, 1.93 mmol) and Cs₂CO₃ (7.527 g, 23.16 mmol). The system was degassed and then charged with nitrogen for 3 times. The mixture was stirred under nitrogen at 80°C in an oil bath for 2 h. The solution was cooled to rt, diluted with EA and separated from the water layer. The EA solution was washed by brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **12-6** (32.4%). +ESI-MS: m/z 322.0 [M + H]⁺.

[0757] To a solution of **12-6** (1.8 g, 5.6 mmol) in THF (100 mL) was added LAH (0.428 g, 1.2 mmol) at -78°C. The solution was stirred for 10 mins. The solution was quenched with H₂O (0.4 mL). The solution was filtered and the filtrate was concentrated to give crude **12-7** (1.3 g, 78.8 %). +ESI-MS: m/z 294.0 [M + H]⁺.

[0758] To a solution of **12-7** (1.3 g, 4.42 mmol) in DMF was added imidazole (0.601 g, 8.84 mmol) at rt. TBSCl (0.978 g, 4.8 mmol) was added. The solution was stirred for 18 h. The solution was washed with water and extracted with EtOAc. The organic phase was concentrated to give **12-8** (1.5 g, 83.3%). +ESI-MS: m/z 408.1 [M + H]⁺.

[0759] Compound **1255** was obtained following the procedure for obtaining compound **1200** by using **12-8** as the starting material. Compound **1255** was obtained as a white solid. +ESI-MS: m/z 511.1 $[M+H]^+$.

EXAMPLE 12-21
Preparation of Compound 1256



[0760] To a solution of **12-9** (3.5 g, 20 mmol) in THF/MeOH (v/v = 1:2, 30 mL) was added NaBH_4 (1.2 g, 32 mmol) at rt. The solution was stirred at rt for 1 h with TLC monitoring. The reaction was quenched by addition of HCl (1.0 N in H_2O) and extracted by EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to give crude **12-10** (3.0 g), which was used in next step without purification. $^1\text{H-NMR}$: CDCl_3 (400MHz): δ = 7.35-7.27 (t, 5 H), 4.40 (s, 2 H), 3.91-3.87 (m, 1 H), 3.63-3.59 (m, 1 H), 2.73-2.66 (m, 2 H), 1.95-1.88 (m, 2 H).

[0761] A solution of **12-10** (3.0 g, 16.8 mmol), 4-hydroxy-3-methoxybenzoic acid (3.01 g, 16.8 mmol), and PPh_3 (6.6 g, 25.2 mmol) in dry THF (50 mL) was stirred at 0°C under a nitrogen atmosphere. The mixture was added dropwise DIAD (5.1 g, 25.2 mmol) over a period of 5 mins. The mixture was stirred under nitrogen at 50°C in an oil bath for 3 h with monitoring by TLC. The solvent was evaporated under reduced pressure and the oil was purified by flash column chromatography (PE/EA=10:1 to 2:1) to give **12-11** (2.5 g) as a white solid.

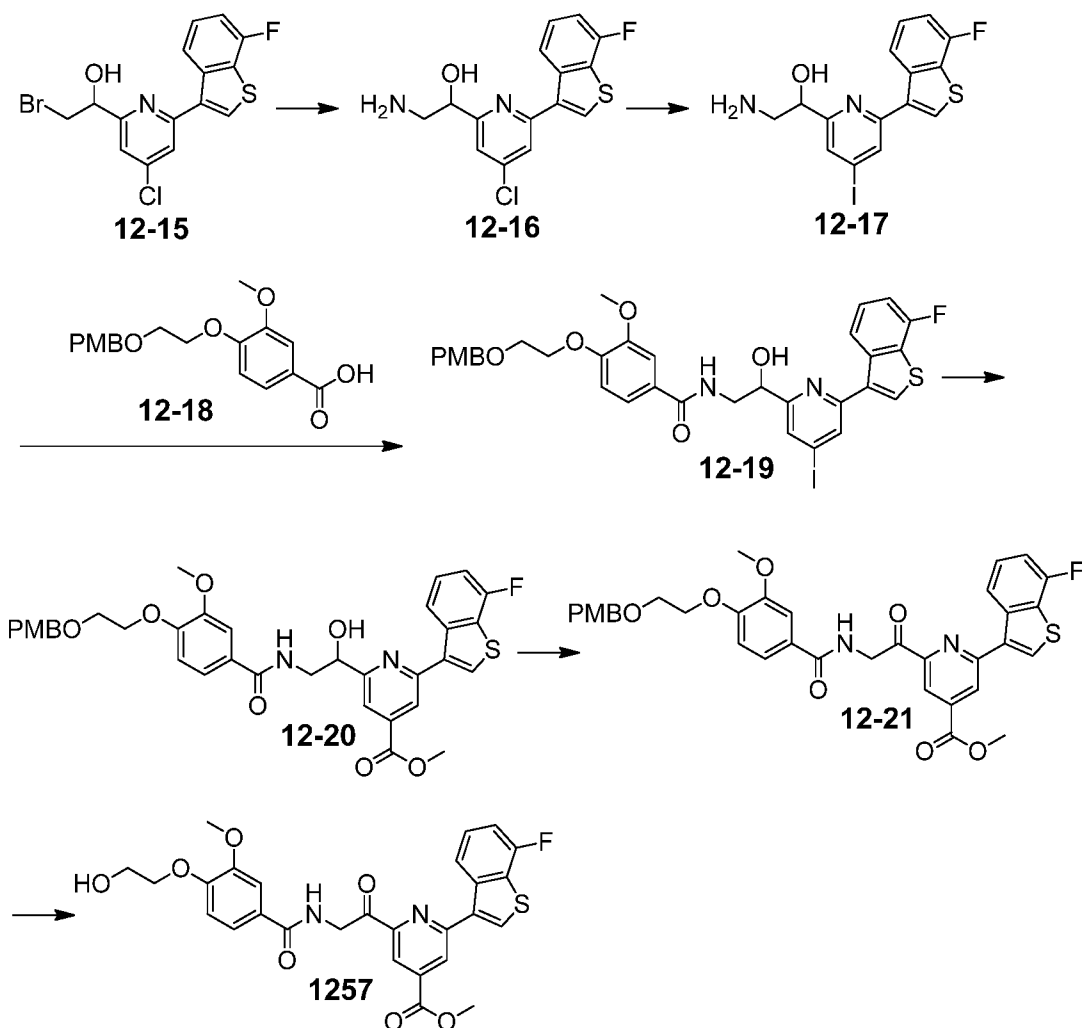
[0762] To a mixture of **12-11** (2.5 g, 7.3 mmol) in MeOH (15 mL) was added Pd/C (10%, 400 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ three times. The mixture was stirred under H₂ (40 psi) at rt for 3 h. The suspension was filtered through a pad of Celite and the pad cake was washed with MeOH. The combined filtrates were concentrated to give crude **12-12** (2.2 g), which was used in next step without purification.

[0763] To a mixture of NaH (320 mg, 13.3 mmol) in DMF (20 mL) was added **12-12** (2.2 g, 8.7 mmol) under 0°C. SEMCl (2.2 g, 13.3 mmol) was added. The mixture was stirred at rt for 2 h with TLC monitoring. The reaction was quenched by addition of H₂O and extracted by EtOAc. The combined organic layers were washed by brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **12-13** (2.9 g).

[0764] A solution of **12-13** (2.9 g, 7.6 mmol) and 2N sodium hydroxide solution (35 mL) in MeOH (35 mL) was stirred under reflux for 1 hour. The mixture was neutralized using 2N hydrochloric acid solution, and extracted with EtOAc. The combined organic solutions were dried (MgSO₄), and evaporated under reduced pressure to give **12-14** (2.0 g). ESI-LCMS: m/z = 391 [M + Na]⁺.

[0765] Compound **1256** was obtained following the procedure for obtaining compound **1215** by using **12-14** and 2-amino-1-(6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)ethanol as the starting materials. Compound **1256** was obtained as a white solid. +ESI-LCMS: m/z = 506.9 [M + H]⁺.

EXAMPLE 12-22
Preparation of Compound 1257



[0766] To a solution of **12-15** (1.5 g, 38.7 mmol) in EtOH (5 mL) was added NH₄OH (4 mL) in a seal tube. The mixture was stirred at 100°C for 1 h. The mixture was diluted with water and extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to the crude product, which was purified by column chromatography to give **12-16** (400 mg). +ESI-MS: m/z 323.0 [M + H]⁺.

[0767] To a solution of **12-16** (400 mg, 1.24 mmol) in EA (5 mL) was added HCl/EA (4 M, 2 mL). The mixture was stirred at rt for 20 mins, and concentrated in vacuum to give the HCl salt. The HCl salt was dissolved in CH₃CN (20 mL), and NaI (1.86 g, 12.4 mmol) was added, and the mixture was stirred at 110°C overnight. The mixture was washed with NaHCO₃ solution, and extracted with EA. The organic layer was dried over sodium

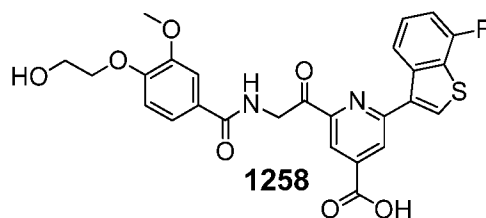
sulfate, and concentrated in vacuum to give the crude product, which was purified by column chromatography to give **12-17** (550 mg). +ESI-MS: m/z 415.0 $[M + H]^+$.

[0768] To a solution of **12-18** (415 mg, 1.25 mmol) in DMF (20 mL) were added DIPEA (645 mg, 5.0 mmol), HATU (475 mg, 1.25 mmol), and the mixture was stirred at rt for 30 mins. Compound **12-17** (514 mg, 1.25 mmol) was added, and the mixture was stirred at rt for 2 h. 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 **12-19** (650 mg). +ESI-MS: m/z 729.1.0 $[M + H]^+$.

[0769] To a solution of **12-19** (0.55 g, 0.76 mmol) in MeOH (20 mL) were added $Pd(PPh_3)_4$ (174 mg, 0.15 mmol) and Et_3N (2.3 g, 2.28 mmol). The mixture was stirred at 80°C under 40 psi of CO atmosphere overnight. The mixture was concentrated in vacuum to give the crude product, which was purified by column chromatography to give **12-20**. (430 mg, yield: 87.2%) +ESI-MS: m/z 661.1 $[M + H]^+$.

[0770] To a solution of **12-20** (520 mg, 0.79 mmol) in DCM (30 mL) was added DMP (1.02 g, 2.36 mmol), and the mixture was stirred at rt for 2 h. The mixture was diluted with EA and washed with water. The organic layer was dried over sodium sulfate, concentrated in vacuum to give **12-21** as white solid. +ESI-MS: m/z 659.1 $[M + H]^+$.

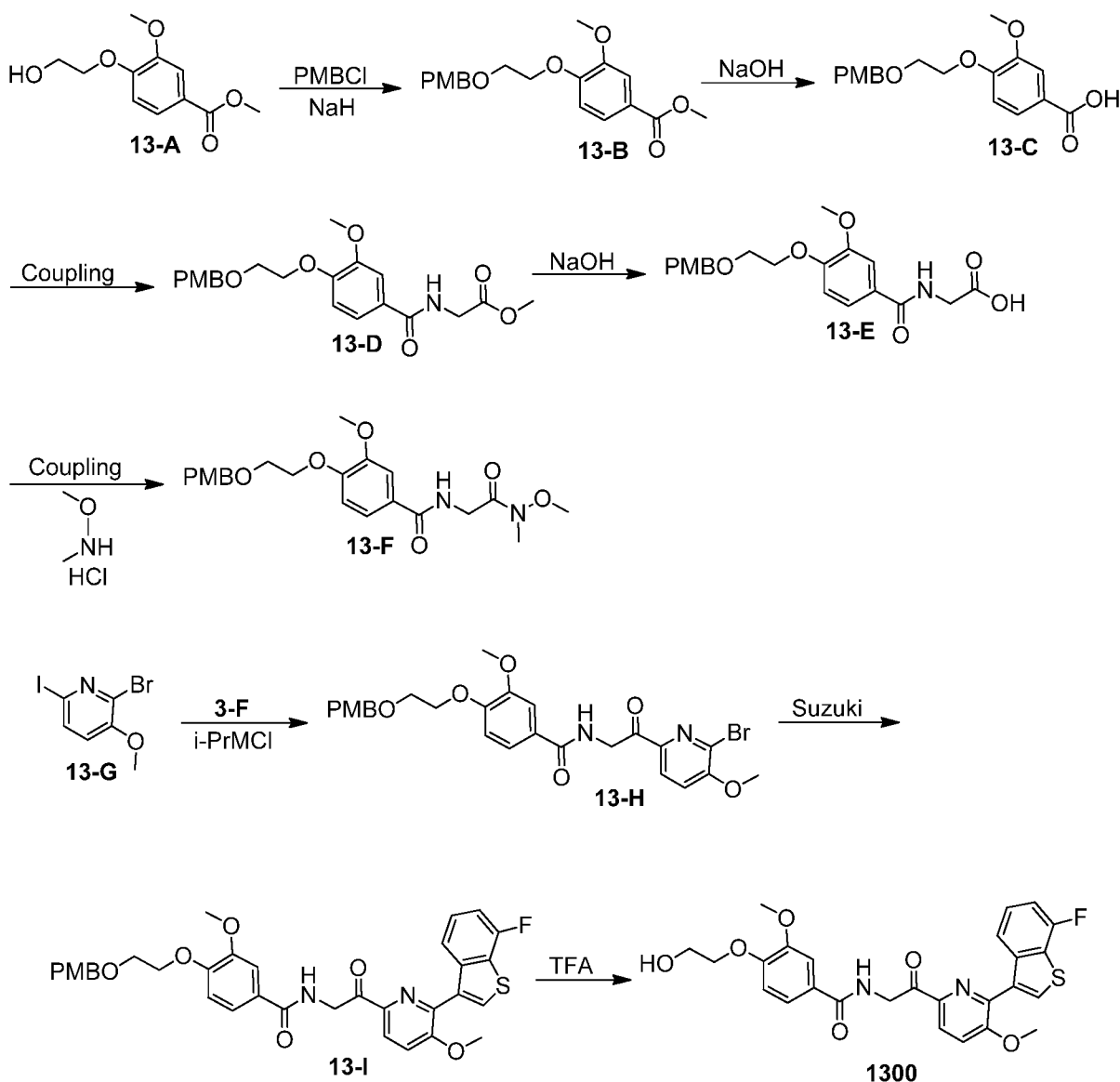
[0771] Compound **12-21** (440 mg, 0.67 mmol) was dissolved in DCM/TFA (1:1, 10 mL), and the mixture was stirred at rt for 5 mins. The mixture was diluted with DCM and the pH of the mixture was adjusted to 7.0 by adding $NaHCO_3$ solution. The organic layer was dried over sodium sulfate and concentrated in vacuum to give the crude product, which was purified by TLC separation to give compound **1257** (23 mg) as a white solid. +ESI-LCMS: $m/z = 538.9 [M + H]^+$.



[0772] To a solution of compound **1257** (180 mg, 0.335 mmol) in THF/ H_2O (2:1, 10 mL) was added LiOH (40 mg, 1.67 mmol), and the mixture was stirred at rt for 15 mins.

The mixture was diluted with water, and the pH of the aqueous layer was adjusted to around 5 by progressively adding NH_4Cl solution. The mixture was extracted with EA. The organic layers were dried over sodium sulfate and concentrated in vacuum to give the crude product, which was purified by prep-HPLC to give compound **1258** (32 mg) as a white solid. +ESI-LCMS: $m/z = 525.1$ $[\text{M} + \text{H}]^+$.

EXAMPLE 13-1
Preparation of Compound 1300



[0773] To a solution of crude **13-A** (10 g, 44.0 mmol) in DMF (150 mL) was added NaH (7.0 g, 0.177 mol). The mixture was stirred at 0°C for 30 mins. PMBCl (11.67 g, 74.8 mmol) was added. The mixture was stirred at rt overnight. The solution was then

diluted with water and extracted with EtOAc. The organic phase was concentrated to give **13-B** (11 g, 87.2%). ⁺ESI-MS: m/z 347.1 [M + H]⁺.

[0774] To a solution of **13-B** (11 g, 31.8 mmol) in MeOH (100 mL) was added KOH (7.0 g, 127 mmol), and stirred at rt overnight. The mixture was extracted with EA, and the pH of the aqueous layer was adjusted to approximately 5 by progressive addition of diluted HCl, followed by extraction with EA. The organic layers were dried over sodium sulfate and concentrated in vacuum to give **13-C** (8.4 g), which was used in the next step without further purification. ¹H-NMR (400MHz, CDCl₃) δ = 8.04 (s, 1H), 7.16 (d, *J*= 8.0 Hz, 1H), 7.59 (s, 1H), 7.30-7.27 (m, 2H), 6.94-6.87 (m, 3H), 4.58 (s, 2H), 4.26 (t, *J*=4.8 Hz, 2H), 3.93 (s, 3H), 3.85 (t, *J*=4.8 Hz, 2H), 3.81 (s, 3H).

[0775] To a solution of **13-C** (6.0 g, 18.0 mmol) in DMF (100 mL) were added HATU (10.3 g, 27 mmol) and DIPEA (7.0 g, 54 mmol). The mixture was stirred at rt for 30 mins. Methyl 2-aminoacetate hydrochloride (2.3 g, 18 mmol) was added and stirred at rt overnight. The mixture was concentrated in vacuum, diluted with water, and extracted with EA. The organic layer was dried over sodium sulfate and concentrated in vacuum to give crude **13-D**, which was purified by column chromatography. ⁺ESI-MS: m/z 404.1 [M + H]⁺.

[0776] To a solution of **13-D** (9.7 g, 24 mmol) in MeOH (100 mL) was added KOH (5.4 g, 96 mmol). The mixture was stirred at rt overnight, and then extracted with EA. The pH of the aqueous layer was adjusted to approximately 5 by progressively adding diluted HCl, followed by extraction with EA. The organic layers were dried over sodium sulfate and concentrated in vacuum to give **13-E** (8.5 g), which was used in the next step without further purification. ¹H NMR (400MHz, *d*-DMSO) δ = 8.70 (t, *J*=6.0Hz, 1H), 7.43 (s, 2H), 7.24 (d, *J*= 8.0 Hz, 2H), 7.01 (d, *J*= 8.0 Hz, 1H), 6.88 (d, *J*= 8.0 Hz, 2H), 5.02 (s, 2H), 4.45 (t, *J*=4.8 Hz, 2H), 4.41 (s, 2H), 3.88 (t, *J*=4.8 Hz, 2H), 3.78 (s, 3H).

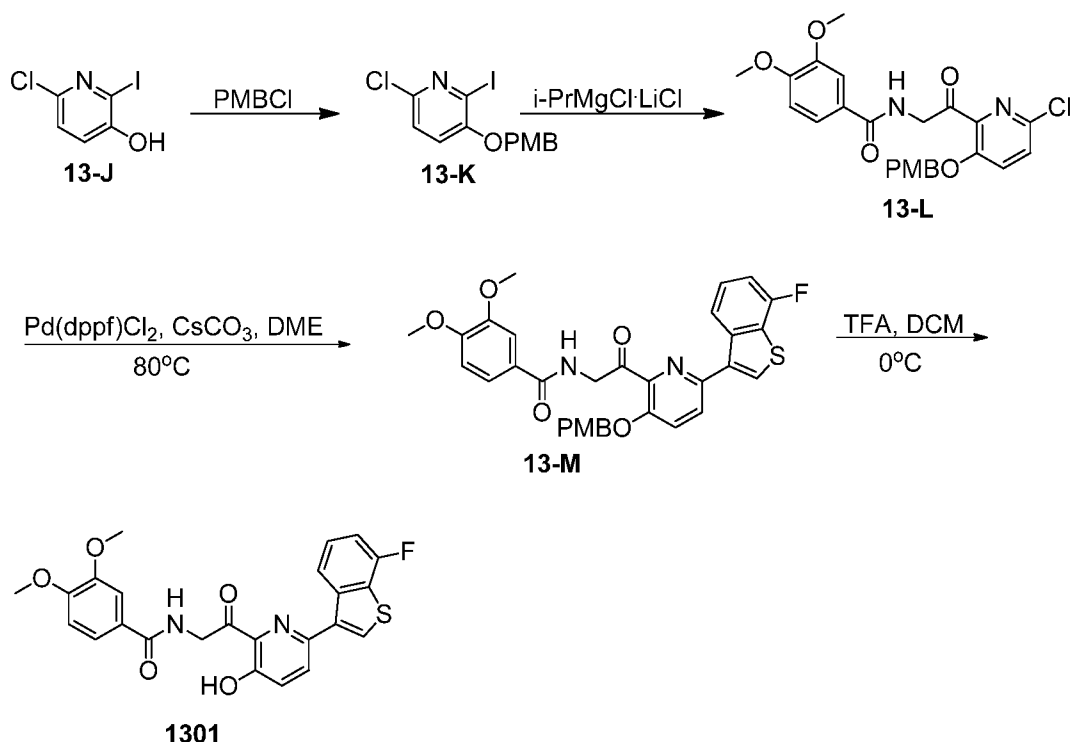
[0777] To a solution of **13-E** (8.5 g, 21.85 mmol) in DMF (200 mL) were added HATU (8.3 g, 21.85 mmol) and Et₃N (8.83 g, 87.4 mmol). The mixture was stirred at rt for 30 mins. N,O-dimethylhydroxylamine hydrochloride (2.12 g, 21.85 mmol) was added, and the mixture was stirred at rt overnight. The mixture was concentrated in vacuum, diluted with water, and extracted with EA. The organic layer was dried over sodium sulfate and concentrated in vacuum to give crude **13-F**, which was purified by column chromatography. ⁺ESI-MS: m/z 433.1 [M + H]⁺.

[0778] To a solution of **13-F** (3.71 g, 8.6 mmol) and **13-G** (2.7 g, 8.6 mmol) in THF (50 mL) was added i-PrMgCl (17.2 mL, 34.4 mmol) in portions. The reaction was quenched after 3 mins with a NH₄Cl solution. The mixture was extracted with EA. The organic phase was dried over sodium sulfate, and then concentrated in vacuum to give the crude product, which was purified by column chromatography to give pure **13-H** (2.4 g). +ESI-MS: m/z 558.1, 560.1 [M +H]⁺.

[0779] To a solution of **13-H** (2.2 g, 3.93 mmol) in dioxane/H₂O (10 : 1) (30 mL) were added Compound **12-C** (1.09 g, 3.93 mmol), Pd(dppf)Cl₂ (288 mg, 0.393 mmol) and KOAc (0.94 g, 11.8 mmol). The mixture was bubbled with nitrogen gas and stirred at 90°C for 3 h. The mixture was diluted with water and extracted with EA. The organic layer was dried over sodium sulfate, and then concentrated in vacuum to give the crude product, which was purified by column chromatography to give **13-I** (1.2 g). +ESI-MS: m/z 631.1 [M +H]⁺.

[0780] Compound **13-I** (200 mg, 0.32 mmol) was dissolved in DCM/TFA (1: 1) (34 mL) and then stirred at rt for 30 mins. The mixture was diluted with DCM and the pH of the mixture was adjusted to 7.0 by addition of a saturated NaHCO₃ 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 compound **1300** (70mg) as a white solid. ¹H NMR: (400MHz, *d*-DMSO): δ = 8.71-8.69 (t, *J*=5.2 Hz, 1 H), 8.25 (d, *J*=8.0 Hz, 1 H), 8.47 (s, 1 H), 8.25 (d, *J*=8.0 Hz, 1 H), 8.09 (d, *J*=8.4 Hz, 1 H), 7.84 (d, *J*=8.8 Hz, 1 H), 7.55-7.51 (m, 3 H), 7.36-7.31 (t, *J*=9.0 Hz, 1 H), 7.06 (d, *J*=8.4 Hz, 1 H), 4.94-4.87 (m, 3 H), 4.06-4.01 (m, 5 H), 3.82 (s, 3 H), 3.77-3.74 (t, *J*=5.0 Hz, 2 H).

EXAMPLE 13-2
Preparation of Compound 1301



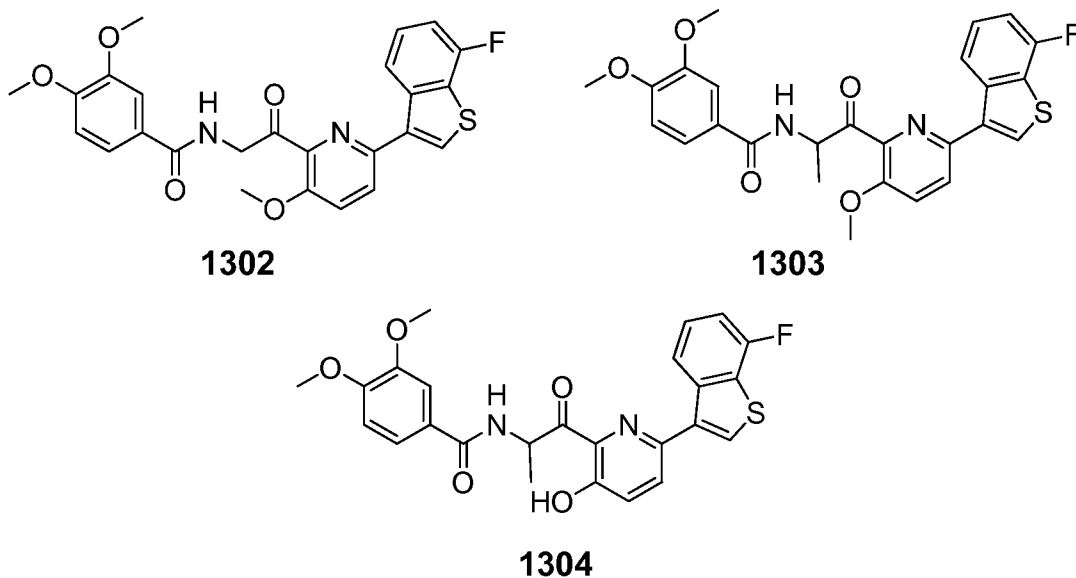
[0781] To a solution of **13-J** (12.7 g, 50 mmol) in DCM (100 mL) was added PMBCl (9.4 g, 60 mmol) and TEA (7.5 g, 75 mmol). This mixture was stirred at rt overnight. The reaction solution was washed with brine, and the organic layer was concentrated to give crude **13-K**, which was used in the next step without further purification. ¹H-NMR: (400MHz, *d*-DMSO): δ = 7.46 (d, *J*=8.8 Hz, 2 H), 7.38 (d, *J*=8.0 Hz, 2H), 6.94 (d, *J*=8.0 Hz, 2H), 5.14 (s, 2 H), 3.73 (s, 3H).

[0782] A solution of **13-K** (3.75 g, 10 mmol) in THF (30 mL) was added *i*-PrMgCl·LiCl (20 mmol) at rt. After 10 mins, the reaction was monitored by TLC. The mixture was diluted with water, and extracted with EA. The solution was evaporated at low pressure to give the crude product. The residue was purified by silica column chromatography using DCM:MeOH= 50:1 as the elute to generate **13-L** (3 g, 64%). +ESI-MS: *m/z* 471.1 [M +H]⁺.

[0783] To a solution of crude **13-L** (2.35 g, 5 mmol) in DME (20 mL) was added 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.39 g, 5 mmol), cesium carbonate (3.25 g, 10 mmol) and Pd(dppf)Cl₂ (109 mg, 0.15 mmol). The reaction

was stirred for 2 h at 80°C under N₂. The solution was filtered, and the filtrate was concentrated by rotary evaporator. The residue was dissolved in DCM, and the solution was washed with brine. The organic phase was evaporated at low pressure to give the crude product. The residue was purified by silica column chromatography with EA:PE = 1:1 as the elute to give **13-M** (2 g, 68%). +ESI-MS: *m/z* 587.1 [M + H]⁺.

[0784] To a solution of **13-M** (440 mg, 0.75 mmol) in dry DCM (5 mL) was added TFA (2 mL) at 0°C. After 1 h, the reaction was monitored by TLC. The reaction solution was washed with brine, and the DCM layer was concentrated by rotary evaporator. The product was purified by prep-TLC with EA: PE = 2:1 as the elute to give **1301** (280 mg, 80%). ¹HNMR (*d*-DMSO) δ = 8.81 (s, 1H), 8.62 (d, *J* = 8 Hz, 1H), 8.48 (s, 1H), 8.20 (d, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.55-7.50 (m, 3H), 7.33 (t, *J* = 8 Hz, 1H), 7.04 (d, *J* = 8 Hz, 1H), 5.03 (s, 2H), 3.79 (s, 6H).

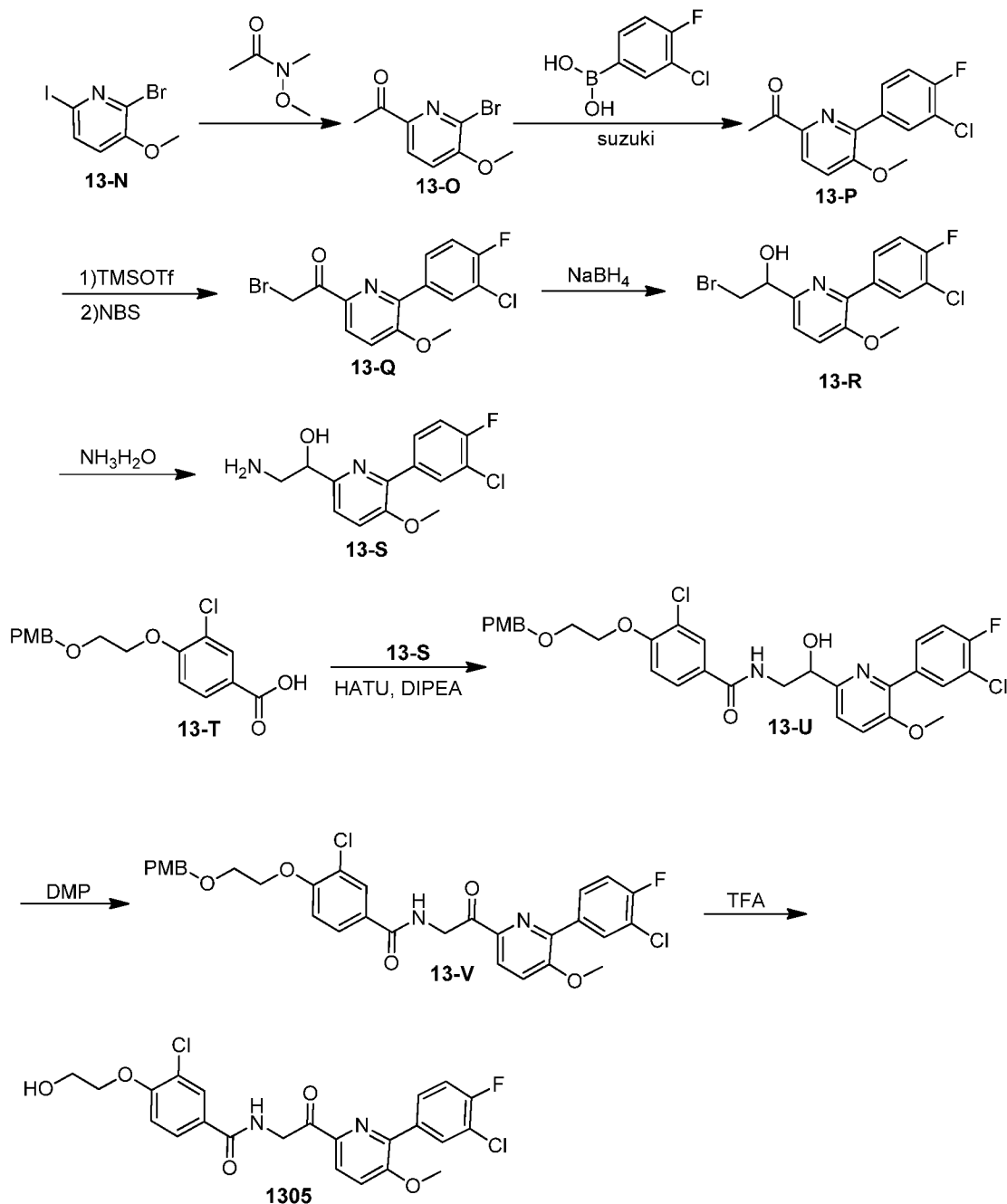


[0785] To a solution of **1301** (93 mg, 0.2 mmol) in DMF (5 mL) was added K₂CO₃ (41 mg, 0.3 mmol) and MeI (28 mg, 0.2 mmol). The reaction was stirred for 1 h. Water (20 mL) was poured into the reaction solution, and the solution was extracted with DCM. The organic layer was concentrated by rotary evaporator. The product was purified by prep-HPLC to give **1302** (15 mg, 17%), **1303** (10 mg) and **1304** (10 mg). Compound **1302**: +ESI-MS: *m/z* 466.9 [M + H]⁺. Compound **1303**: ¹H-NMR (*d*-DMSO) δ = 8.60 (dd, *J* = 8 Hz, *J* = 1.2 Hz, 2H), 8.39 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 4 Hz, 1H), 7.51-7.49 (m, 2H), 7.44 (s, 1H), 7.33-7.31 (m, 1H), 7.99 (d, *J* = 8 Hz, 1H), 5.78-5.74 (m, 1H), 3.90

(s, 3H), 3.77 (d, $J = 6$ Hz, 6H). ESI-MS: m/z 495.0 $[M+H]^+$. Compound **1304**: +ESI-MS: m/z 480.9 $[M+H]^+$.

EXAMPLE 13-3

Preparation of Compound 1305



[0786] To a solution of **13-N** (5 g, 16.0 mmol) and Weinreb amide (1.6 g, 16.0 mmol) in THF (10 mL) was added $i\text{-PrMgCl}$ (10 mL, 19.2 mmol). The solution was stirred at rt for 5 mins and the concentrated. The solution was acidified to pH=7 with aq. NH_4Cl ,

and the aqueous layer was extracted with DCM. The organic layers were combined and purified by column chromatography with PE: EA=5:1 as the elute to give **13-O** (1.9 g, 51.9 %). $^1\text{H-NMR}$ (d -DMSO) δ = 7.97 (d, J =8.4 Hz, 1H), 7.63 (d, J =8.4 Hz, 1H), 3.97 (s, 3H), 2.53 (s, 3H).

[0787] To a solution of **13-O** (700 mg, 1.12 mmol), (3-chloro-4-fluorophenyl)boronic acid (336 mg, 1.2 mmol) and Cs_2CO_3 (24.3 g, 74.2 mmol) in dioxane (20 mL) and H_2O (2 mL) were added $\text{Pd}(\text{dppf})_2\text{Cl}_2$ (812 mg, 1.11 mmol). The mixture was degassed and then charged with nitrogen 3 times. The mixture was stirred under nitrogen at 80°C using an oil bath for 5 h. The solution was cooled to rt, diluted with EA and separated from the aqueous layer. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column to give **13-P** (7.3 g, 70.5 %), which used for next step without further purification. $^1\text{H-NMR}$ (d -DMSO) δ = 8.11 (d, J = 7.2 Hz, 1H), 8.00-7.96 (m, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H), 2.62 (s, 3H).

[0788] To a solution of **13-P** (1.8 g, 6.4 mmol) in DCM (15 mL), were added DIPEA (3.3 g, 25.8 mmol) and TMSOTf (4.3 g, 19.4 mmol). The mixture was stirred at rt for 30 mins, and the solution was extracted with DCM (20 mL). The organic phase was evaporated at low pressure to generate the crude residue. The residue was treated with a solution of NBS (1.12 g, 6.4 mmol) in THF (10 mL) and H_2O (10 mL). After 10 mins, the solution was quenched by an aqueous NaHCO_3 solution and extracted with EtOAc. The combined organic layers were washed by saturated $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried over Na_2SO_4 and concentrated to give crude **13-Q** (2.0 g) which can be used in the next step without further purification. $^1\text{H-NMR}$ (CDCl_3) δ = 8.11 (d, J = 8.0 Hz, 2H), 7.95-7.93 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.25-7.21 (m, 1H), 4.85 (s, 2H), 3.99 (s, 3H).

[0789] To a solution of crude **13-Q** (7.0 g, 19.6 mmol) in a mixture of THF (20 mL) and EtOH (8 mL) were added NaBH_4 (1.1 g, 19.6 mmol) at 0°C . The mixture was stirred at 0°C for 30 mins. The reaction was quenched by the addition of H_2O and extracted by EtOAc. The combined organic layers were washed using brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column to give **13-R** (4.0 g, 57.1 %). $^1\text{H-NMR}$ (CDCl_3) δ = 8.06 (d, J = 7.2 Hz, 1H), 7.09-7.87 (m, 1H), 7.36-7.32(m, 2H), 7.20 (t, J = 8.8 Hz, 1H), 5.00-4.95 (m, 1H), 4.08 (d, J = 9.6 Hz, 1H), 3.91 (s, 3H), 3.79-3.70 (m, 2H).

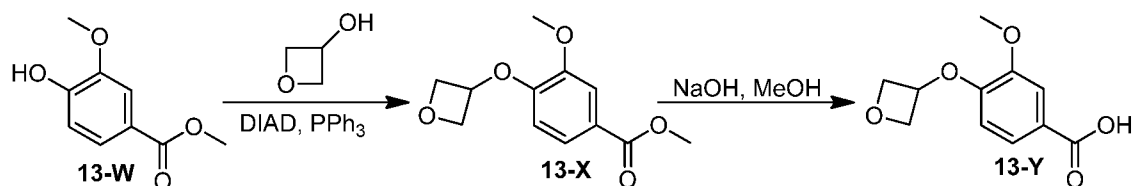
[0790] A mixture of **13-R** (720 mg, 2.0 mmol), K_2CO_3 (552 mg, 4.0 mmol) and saturated $NH_3/EtOH$ (15/15 mL) in a sealed tube was stirred at ambient temperature for 20 mins, then heated to $50^\circ C$ for 10 h. The solvent was removed under reduced pressure to give crude **13-S** (0.6 g), which used for next step without further purification. ^1H -NMR ($CDCl_3$) δ = 8.05 (d, J = 8.0 Hz, 1H), 7.88-7.87 (m, 1H), 7.36-7.18 (m, 3H), 4.75-4.72 (m, 1H), 3.90 (s, 3H), 3.17-3.13 (m, 1H), 2.96-2.91 (m, 1H).

[0791] To a solution of **13-T** (336 mg, 1.0 mmol), HATU (570 mg, 1.5 mmol) and DIPEA (320 mg, 2.5 mmol) in anhydrous DCM (10 mL) was added **13-S** (296 mg, 1.0 mmol) at $25^\circ C$. The solution was stirred for 3 h at $25^\circ C$. The mixture was diluted with 1.0 N aqueous $NaHCO_3$ solution, and extracted with DCM. The combined organic layers were washed using brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified on a silica gel column using PE:EA=2:1 to 1:3 as the elute to give crude **13-U** (450 mg) as a white solid. +ESI-LCMS: m/z = 615.2 $[M + H]^+$.

[0792] To a solution of **13-U** (450 mg, 0.73 mmol) in DCM (6 mL) was added DMP (600 mg, 1.41 mmol). The mixture was stirred at rt for 30 mins with TLC monitoring. The solution was quenched by an aqueous $NaHCO_3$ solution and extracted by EtOAc. The combined organic layers were washed by saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column using PE:EA=2:1 to 1:1 as the elute to give **13-V** (300 mg). +ESI-LCMS: m/z = 613.1 $[M + H]^+$.

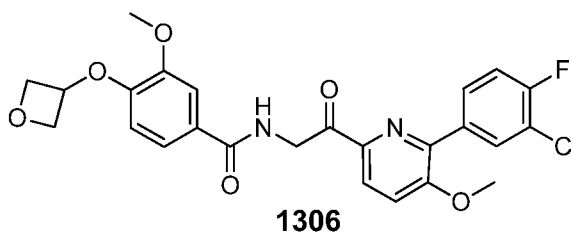
[0793] To a solution of **13-V** (300 mg, 0.49 mmol) in DCM (5 mL) was added TFA (5 mL) at rt. The mixture was stirred at rt for 30 mins with TLC monitoring, quenched by an aqueous $NaHCO_3$ solution and extracted using DCM. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give compound **1305** (80 mg) as a white solid. +ESI-LCMS: m/z = 493.0 $[M + H]^+$.

EXAMPLE 13-4 Preparation of Compound 13-Y



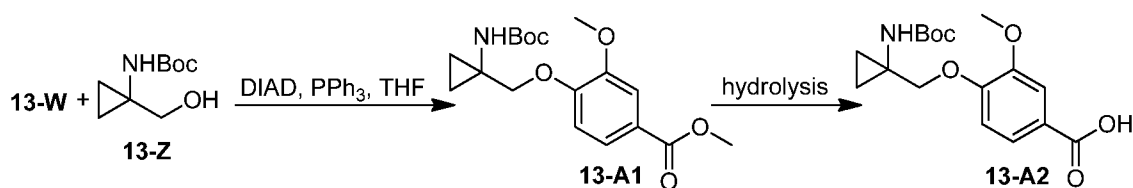
[0794] To a solution of **13-W** (1 g, 5.95 mmol) and oxetan-3-ol (0.484 g, 6.54 mmol) in THF (10 mL) were added DEAD (1.243 g, 7.14 mmol) and PPh₃ (1.87 g, 7.14 mmol). The solution was heated to reflux and stirred for 15 h. The solution was diluted with brine and extracted with EtOAc. The organic phase was concentrated, and the residue was purified by chromatography to give **13-X** (500 mg, 35.7%).

[0795] To a solution of **13-X** (500 mg, 2.1 mmol) in MeOH (5 mL) was added NaOH aqueous (5 mL, 1M). The mixture was stirred for 4 h at 60°C, and the cooled to rt. The mixture was acidified to pH=3 by addition of 1N HCl solution, and extracted with EtOAc. The organic phase was dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to give **13-Y** (250 mg, 53.0%).



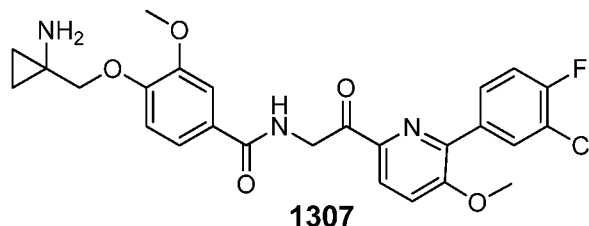
[0796] Compound **1306** was obtained following the procedure for obtaining compound **1351** by using **13-Y** and 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol as the starting materials. Compound **1306** was obtained as a white solid (40 mg, 26.8 %). +ESI-MS: m/z 500.9 [M+H]⁺.

EXAMPLE 13-5 **Preparation of Compound 13-A2**

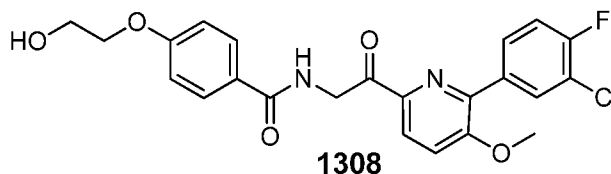


[0797] To a solution of **13-W** (567 mg, 3.13 mmol) in THF (30 mL) was added **3-Z** (750 mg, 3.75 mmol) and PPh₃ (982.5 mg, 3.75 mmol). The mixture was stirred at rt for 30 mins. DIAD (757.5 mg, 3.75 mmol) was added, and the mixture was stirred at 70°C overnight. The mixture was diluted with EtOAc and washed with brine. The organic layers were dried over sodium sulfate and concentrated in vacuum to give crude **13-A1**, which was purified by column chromatography to give purified **13-A1** (600 mg). +ESI-MS: m/z 352.1 [M+H]⁺.

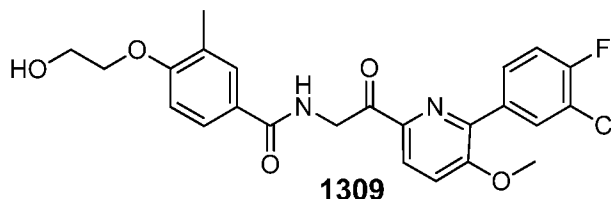
[0798] To a solution of **13-A1** (300 mg, 1.64 mmol) in EtOH/H₂O (2:1) 10 mL was added KOH (460 mg, 8.24 mmol), and the mixture was stirred at 50°C for 1 h. The mixture was extracted with EA, and the pH of the aqueous layer was adjusted to approximately 5 by adding a NaHCO₃ solution, then extracted with EA. The organic layers were dried over sodium sulfate and concentrated in vacuum to give **13-A2** (150 mg). +ESI-MS: m/z 338.1 [M+H]⁺.



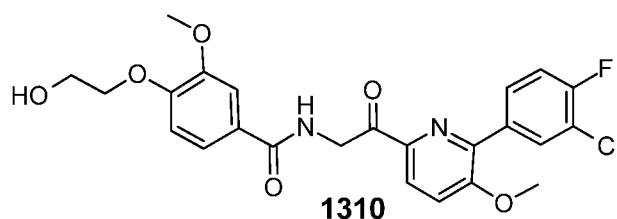
[0799] Compound **1307** was obtained following the procedure for obtaining compound **1351** by using **13-A2** and 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol as the starting materials. Compound **1307** was obtained as a white solid. +ESI-MS: m/z 338.1 [M+H]⁺.



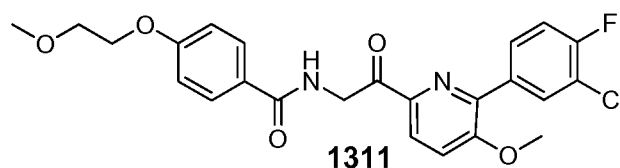
[0800] Compound **1308** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxybenzoate as the starting materials. Compound **1308** was obtained as a white solid. +ESI-MS: m/z 338.1 [M+H]⁺.



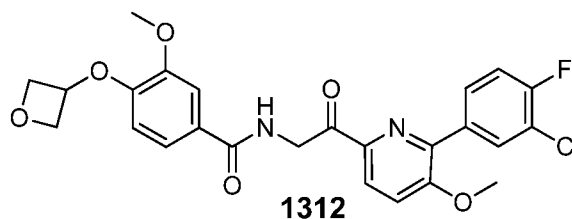
[0801] Compound **1309** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-(2-hydroxyethoxy)-3-methylbenzoate as the starting materials. Compound **1309** was obtained as a white solid. +ESI-MS: m/z 473.1 [M+H]⁺.



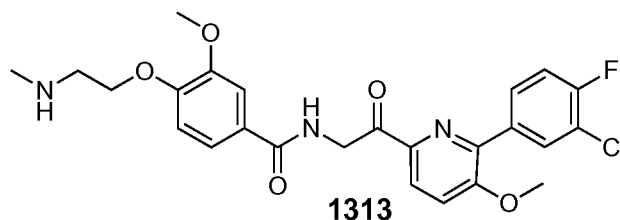
[0802] Compound **1310** was obtained following the procedure for obtaining compound **1300** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxybenzoate as the starting materials. Compound **1310** was obtained as a white solid. +ESI-MS: m/z 489.1 $[M+H]^+$.



[0803] Compound **1311** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxybenzoate as the starting materials. Compound **1311** was obtained as a white solid. +ESI-MS: m/z 473.1 $[M+H]^+$.

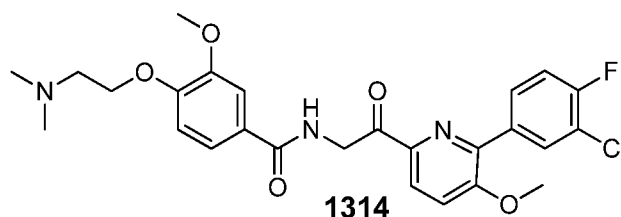


[0804] Compound **1312** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and 3-methoxy-4-(oxetan-3-yloxy) benzoic acid as the starting materials. Compound **1312** was obtained as a white solid (40 mg, 26.8 %). +ESI-MS: m/z 500.9 $[M+H]^+$.

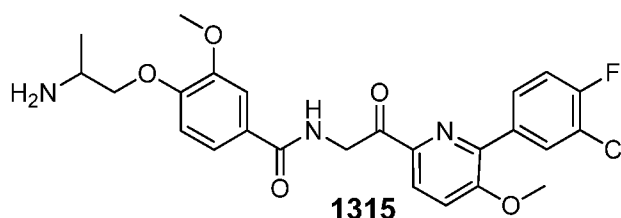


[0805] Compound **1313** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl)

ethanol and methyl 4-hydroxy-3-methoxybenzoate as the starting materials. Compound **1313** was obtained as a white solid (15 mg, 18.07 %). +ESI-MS: m/z 501.9 $[M + H]^+$.



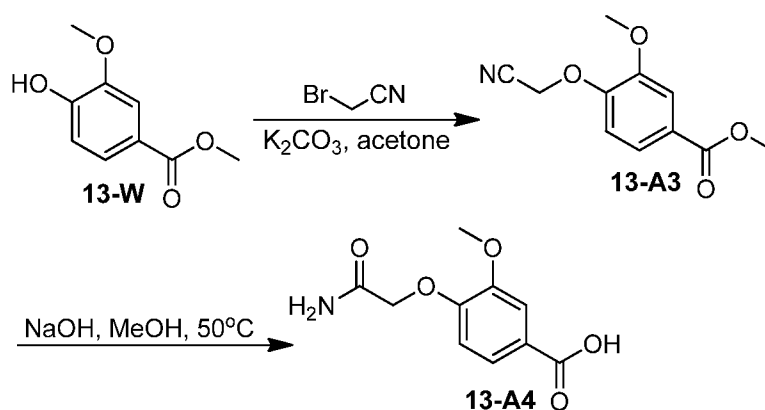
[0806] Compound **1314** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methoxybenzoate as the starting materials. Compound **1314** was obtained as a white solid (20 mg, 18.07 %). +ESI-MS: m/z 516.1 $[M + H]^+$.



[0807] Compound **1315** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methoxybenzoate as the starting materials. Compound **1315** was obtained as a white solid (30 mg, 20.13 %). +ESI-MS: m/z 502.1 $[M + H]^+$.

EXAMPLE 13-6

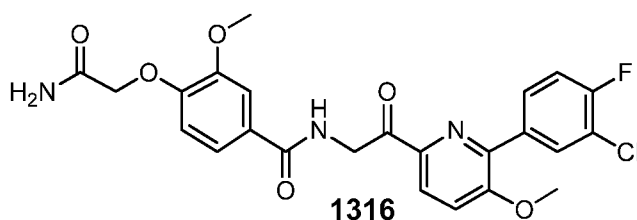
Preparation of Compound 13-A4



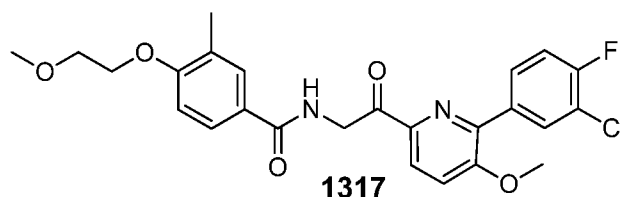
[0808] To a solution of **13-W** (10 g, 54.9 mmol) and 2-bromoacetonitrile (19.7 g, 165 mmol) in acetone (100 mL) were added K_2CO_3 (14.9 g, 108 mmol) at rt. The solution

was heated to reflux and stirred for 4 h. The solid was removed by filtration and the filtrate was concentrated to give **13-A3** (10 g, 82.4%). +ESI-MS: m/z 222.0 $[M + H]^+$.

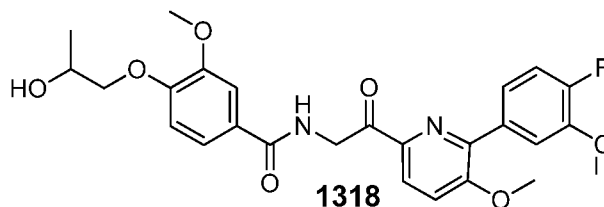
[0809] To a solution of **13-A3** (4 g, 18.09 mmol) in methanol/THF (30 mL/30mL) was added aqueous NaOH solution (36 mL, 1M). The mixture was stirred for 2 h at 60°C. The solution was cooled to rt and acidified to pH=3 by adding 1N HCl solution. The solid was collected by filtration, and the cake was washed with EtOAc and dried to give **13-A4** (1.2 g, 29.4%). +ESI-MS: m/z 226.0 $[M + H]^+$.



[0810] Compound **1316** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and compound **13-A4** as the starting materials. Compound **1316** was obtained as a white solid (25 mg, 16.8 %). +ESI-MS: m/z 501.9 $[M + H]^+$.

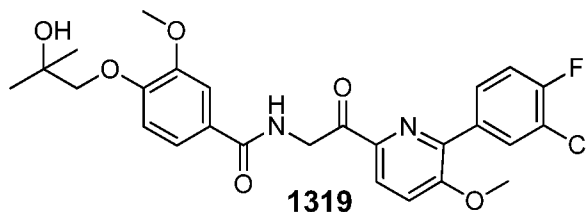


[0811] Compound **1317** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methylbenzoate as the starting materials. Compound **1317** was obtained as a white solid. +ESI-MS: m/z = 487.1 $[M + H]^+$.



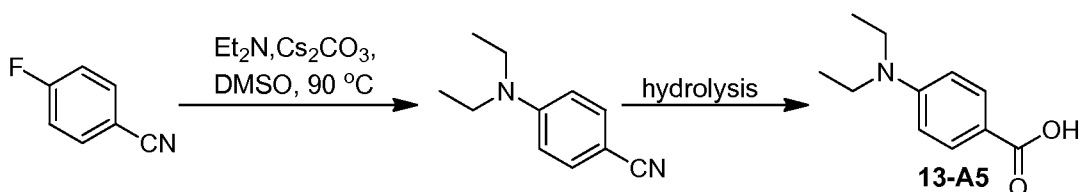
[0812] Compound **1318** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol

ethanol and methyl 4-hydroxy-3-methylbenzoate as the starting materials. Compound **1318** was obtained as a white solid. +ESI-MS: m/z 503.0 $[M + H]^+$.

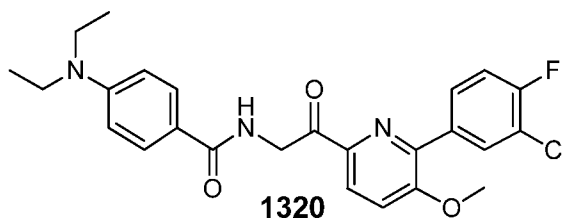


[0813] Compound **1319** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methylbenzoate as the starting materials. Compound **1319** was obtained as a white solid. +ESI-MS: m/z 517.0 $[M + H]^+$.

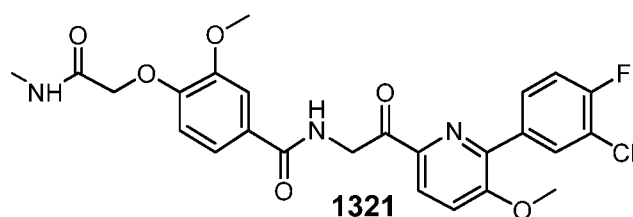
EXAMPLE 13-7
Preparation of Compound 13-A5



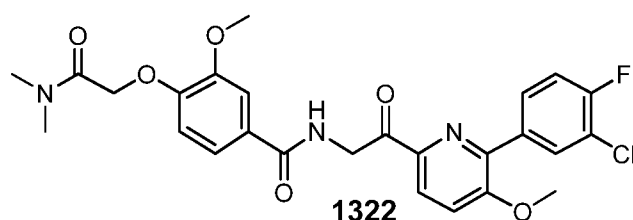
[0814] Compound **13-A5** was prepared according to the procedure in Shinozuka et al., *Chemistry Letters* (2006) 35(10):1090-1091, which is hereby incorporated by reference for the limited purpose of the preparation of compound **13-A5**.



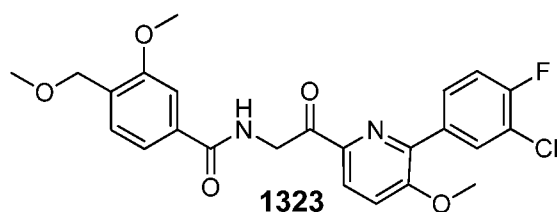
[0815] Compound **1320** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and **13-A5** as the starting materials. Compound **1320** was obtained as a white solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 8.15 (dd, J =2.0, 7.5 Hz, 1H), 8.10 (d, J =8.5 Hz, 1H), 8.03 - 7.98 (m, 1H), 7.78 (d, J =9.0 Hz, 2H), 7.41 (d, J =8.5 Hz, 1H), 7.26 - 7.23 (m, 1H), 7.00 (br. s., 1H), 6.67 (d, J =9.0 Hz, 2H), 5.20 (d, J =4.5 Hz, 2H), 4.00 (s, 3H), 3.42 (q, J =7.0 Hz, 4H), 1.20 (t, J =7.0 Hz, 6H).



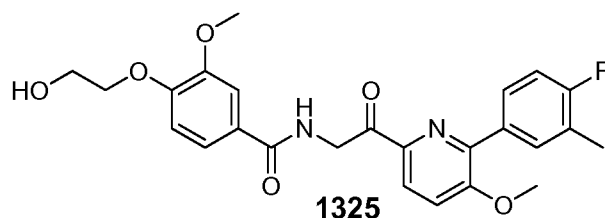
[0816] Compound **1321** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methylbenzoate as the starting materials. Compound **1321** was obtained as a white solid. +ESI-MS: m/z 516.0 $[M + H]^+$;



[0817] Compound **1322** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methylbenzoate as the starting materials. Compound **1322** was obtained as a white solid. +ESI-MS: m/z 529.9 $[M + H]^+$.



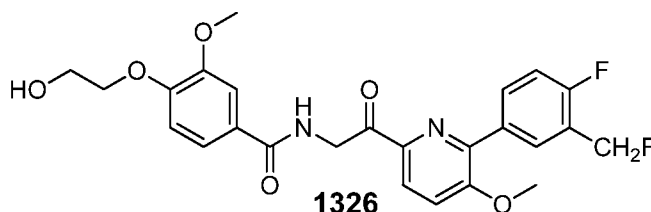
[0818] Compound **1323** was obtained following the procedure for obtaining compound **1351** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and 3-methoxy-4-(methoxymethyl)benzoic acid as the starting materials. Compound **1323** was obtained as a white solid (130 mg). +ESI-MS: m/z 473.1 $[M + H]^+$.



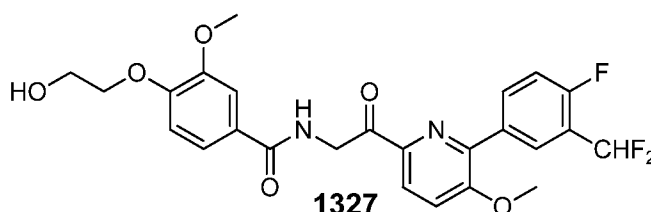
[0819] To a stirred solution of **13-H** (150 mg, 0.267 mmol) in dioxane/ H_2O (50 mL) was added (4-fluoro-3-methylphenyl)boronic acid (51 mg, 0.3 mmol), KF (48 mg, 0.8

mmol) and Pd(dppf)Cl₂ (6.5 mg, 0.008 mmol). The mixture was stirred at 80°C for 2 h. The solution was evaporated and purified by column chromatography gel eluted with PE:acetone=8:1 as the elute to give an intermediate compound (150 mg, 52.9 %). +ESI-MS: m/z 589.2 [M + H]⁺.

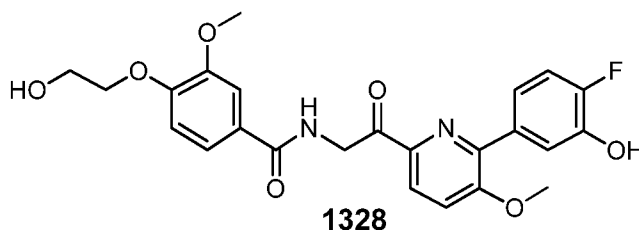
[0820] To a solution of the intermediate compound (150 mg, 0.34 mmol) in DCM (20 mL) was added TFA (2 mL). The mixture was stirred at rt for 5 mins (as determined by TLC, PE: EA=2:1). After conversion, the solution was diluted with CH₂Cl₂, and washed with saturated NaHCO₃ solution. The organic phase was concentrated to give crude compound **1325**, which was purified by prep-HPLC to give purified compound **1325** (32 mg, 16.2 %). +ESI-MS: m/z 469.2 [M + H]⁺;



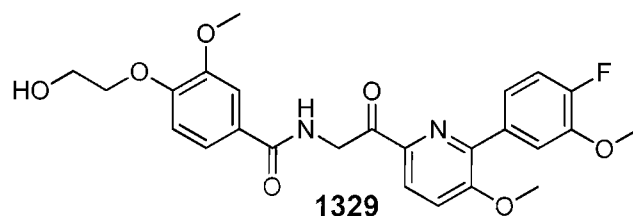
[0821] Compound **1326** was obtained following the procedure for obtaining compound **1325** by using 2-(4-fluoro-3-(fluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting material. Compound **1326** was obtained as a white solid. +ESI-MS: m/z 487.1 [M + H]⁺.



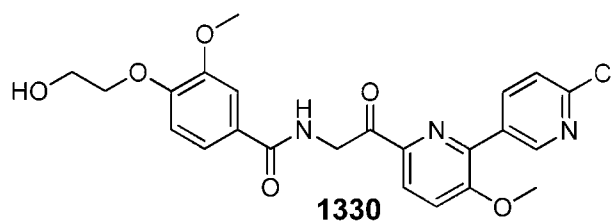
[0822] Compound **1327** was obtained following the procedure for obtaining compound **1325** by using 2-(3-(difluoromethyl)-4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting material. Compound **1327** was obtained as a white solid. +ESI-MS: m/z 505.1 [M + H]⁺.



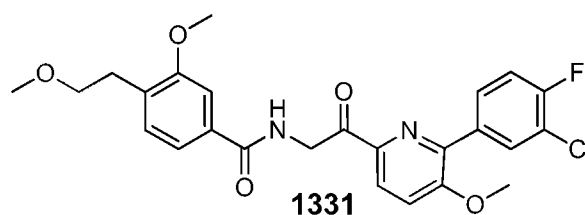
[0823] Compound **1328** was obtained following the procedure for obtaining Compound **1325** by using 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol as the starting material. Compound **1328** was obtained as a white solid. +ESI-MS: m/z 471.1 $[M + H]^+$.



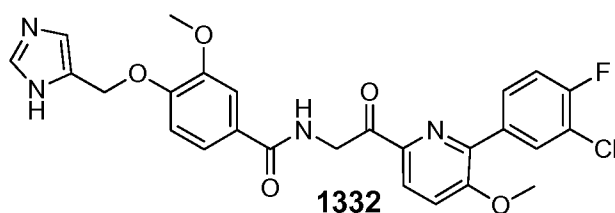
[0824] Compound **1329** was obtained following the procedure for obtaining compound **1325** by using 2-(4-fluoro-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting material. Compound **1329** was obtained as a white solid. +ESI-MS: m/z 485.1 $[M + H]^+$.



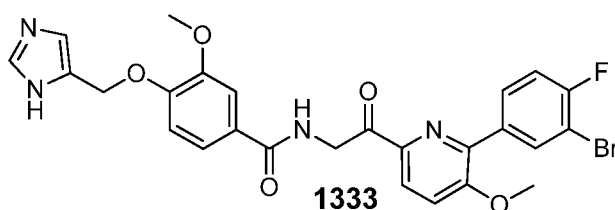
[0825] Compound **1330** was obtained following the procedure for obtaining compound **1325** by using 2-(4-fluoro-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting material. Compound **1330** was obtained as a white solid. +ESI-MS: m/z 472.1 $[M + H]^+$.



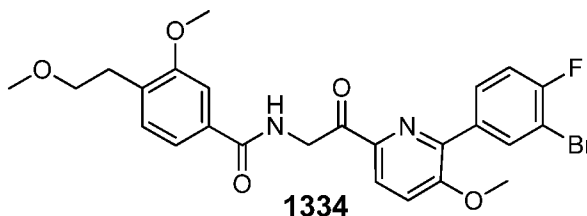
[0826] Compound **1331** was obtained following the procedure for obtaining compound **1325** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and 3-methoxy-4-(2-methoxyethyl) benzoic acid as the starting materials. Compound **1331** was obtained as a white solid. +ESI-MS: m/z = 487.1 $[M + H]^+$.



[0827] Compound **1332** was obtained following the procedure for obtaining compound **1325** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methoxybenzoate as the starting materials. Compound **1332** was obtained as a white solid. +ESI-MS: $m/z = 525.1$ $[M + H]^+$.

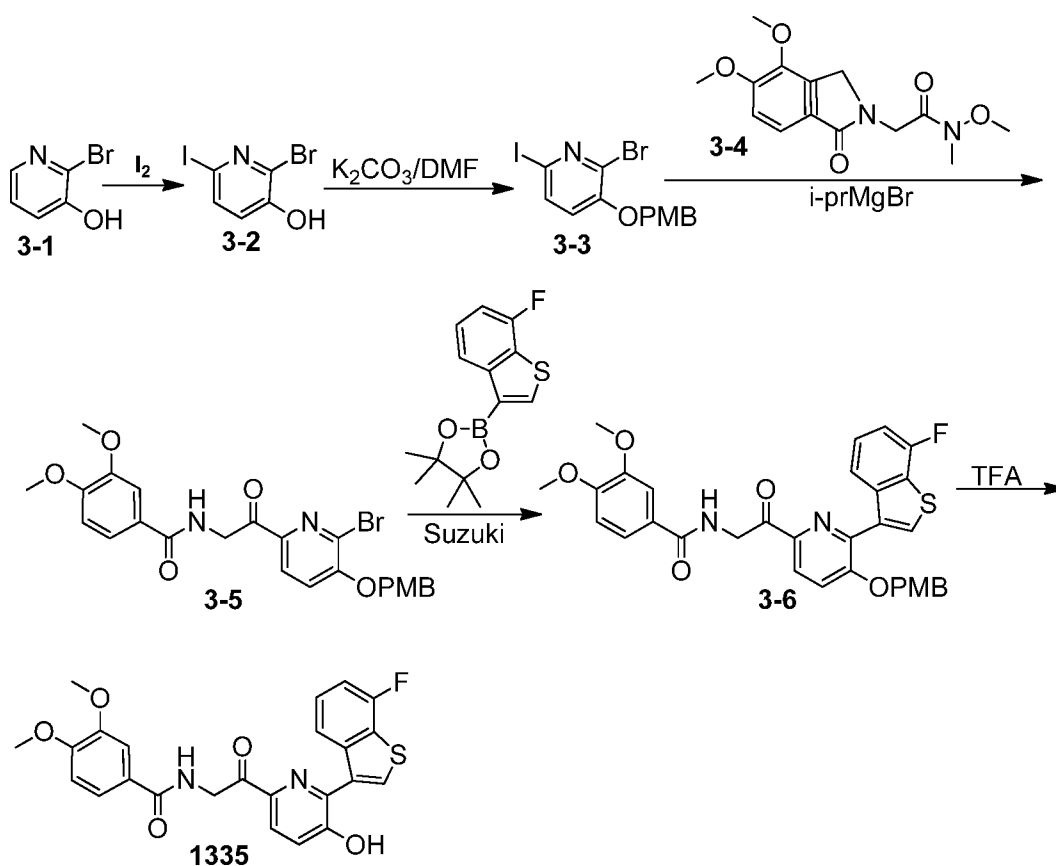


[0828] Compound **1333** was obtained following the procedure for obtaining compound **1325** by using 2-amino-1-(6-(3-bromo-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methoxybenzoate as the starting materials. Compound **1333** was obtained as a white solid. +ESI-MS: $m/z = 568.0, 570.0$ $[M + H]^+$.



[0829] Compound **1334** was obtained following the procedure for obtaining compound **1325** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and methyl 4-hydroxy-3-methoxybenzoate as the starting materials. Compound **1334** was obtained as a white solid. +ESI-MS: $m/z = 531.0$ $[M + H]^+$.

EXAMPLE 13-8
Preparation of Compound 1335

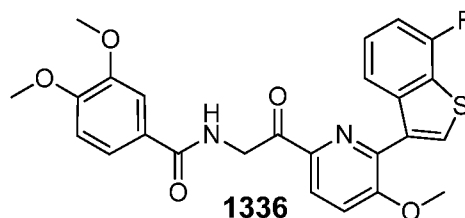


[0830] Compounds **3-2** and **3-3** were prepared according to procedures provided in PCT Publication Nos. WO 2011/109261 and WO 2011/068211, respectively, which are hereby incorporated by reference for the limited purpose of their respective disclosures of the preparation of compound **3-2** and **3-3**.

[0831] To a solution of crude **3-3** (500 mg, 1.2 mmol) in THF (10 mL) was added **3-4** (338 mg, 1.2 mmol) and *i*-PrMgCl (2.4 mL, 4.8 mmol). The solution was stirred at rt for 5 mins. The solution was quenched by aq.NH₄Cl and the aqueous layer was extracted with DCM. The organic layer was combined and purified by column chromatograph gel eluted with PE:EA=1:3 to give **3-5** (0.30 g, yield: 48.6%). ¹H NMR (400 MHz, d-DMSO) δ = 8.60 - 8.76 (m, 1 H), 8.02 (d, *J*=8.38 Hz, 1 H), 7.79 (d, *J*=8.38 Hz, 1 H), 7.36 - 7.56 (m, 5 H), 6.94 - 7.07 (m, 4 H), 5.31 (s, 2 H), 4.79 (d, *J*=5.51 Hz, 2 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.77 (s, 3 H).

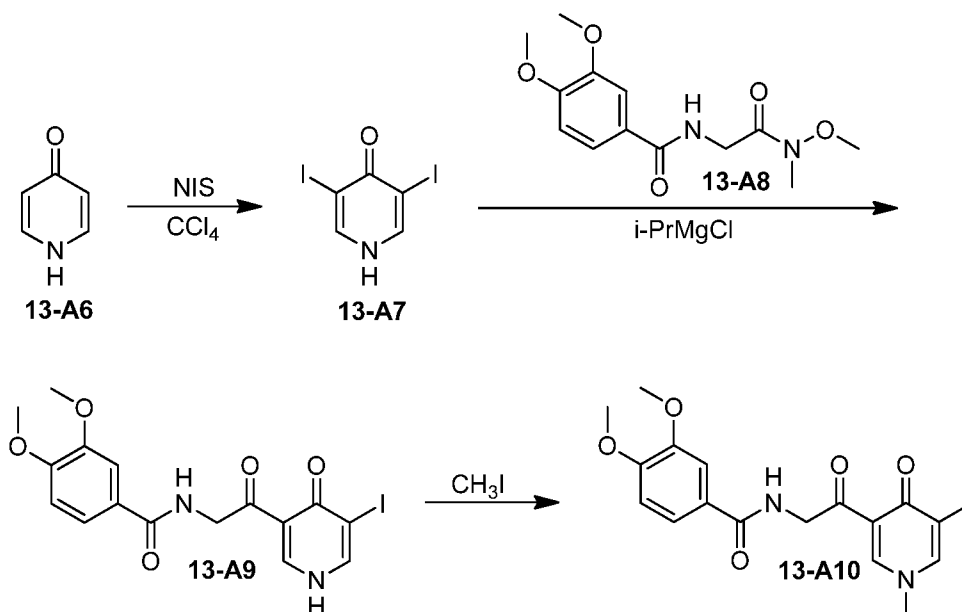
[0832] To a solution of crude **3-5** (200mg, 0.39 mmol) in DME:H₂O=10:1 (5 mL) under N₂ was added Cs₂CO₃ (381 mg, 1.17 mmol), Pd(dppf)₂Cl₂ (8.6 mg, 0.01 mmol) and the dioxaborolane (162.6 mg, 0.58 mmol). The mixture was heated to 85°C for 3 h. The reaction was monitored by TLC (PE:EA=1:1). After conversion completed, the solvent was evaporated and the residue was purified by column chromatograph gel eluted with PE:EA=1:1 to give **3-6** (20 mg, yield: 8.7%).

[0833] To a stirred solution of **3-6** (200 mg, 0.34 mmol) in dry DCM (5 mL) was added TFA (0.2 mL). After complete conversion, the mixture was washed by saturated sodium carbonate. The organic phase was concentrated to dryness and purified by prep-HPLC to afford compound **1335** (10 mg, 6.3 %). +ESI-MS: m/z = 467.1 [M + H]⁺.



[0834] Compound **1336** was obtained following the procedure for obtaining compound **1300** by using N-(2-(6-bromo-5-methoxypyridin-2-yl)-2-oxoethyl)-3,4-dimethoxybenzamide and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1336** was obtained as a white solid. +ESI-MS: m/z = 481.1 [M + H]⁺.

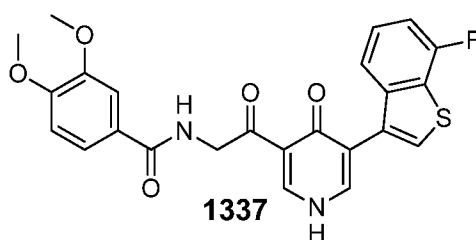
EXAMPLE 13-9
Preparation of Compounds 13-A9 and 13-A10



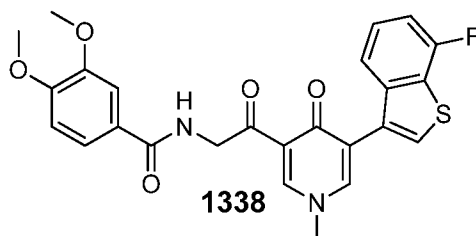
[0835] To a stirred solution of **13-A6** (1.0 g, 10.5 mmol) in CCl₄ (10 mL) was added NIS (4.7 g, 21 mmol), and the mixture was heated to reflux for 12 h. The solution was evaporated and dissolved with DCM. The solution was acidified to pH=8 with aqueous NaS₂O₃, and the aqueous layer was extracted with DCM. The organic layer was combined and purified by column chromatography gel eluted with PE:EA=1:3 as the elute to give **13-A7** (2.0 g, 55.6%). +ESI-MS: $m/z = 347.8 [M + H]^+$.

[0836] To a solution of crude **13-A7** (1.0 g, 2.7 mmol) in THF (10 mL) was added **13-A8** (0.77 g, 2.7 mmol) and i-PrMgBr (7.7 mL, 10 mmol). The solution was stirred at rt for 5 mins and then evaporated. The solution was acidified to pH=8 with aqueous NH₄Cl, and the aqueous layer was extracted with DCM. The organic layer was combined and purified by column chromatography gel with PE: EtOAc=1:1 as the elute to give **13-A9** (0.5 g, 41.7%). +ESI-MS: $m/z = 442.0 [M + H]^+$.

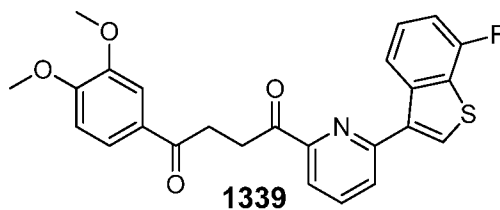
[0837] To a solution of **13-A9** (0.5 g, 1.1 mmol) in DMF (10 mL) was added K₂CO₃ (455.4 mg, 3.3 mmol) and MeI (156 mg, 1.1 mmol). After 30 mins, the solution was evaporated and purified by column chromatography gel eluted with PE:EA=1:5 as the elute to give **13-A10** (0.3 g, 60.1%). +ESI-MS: $m/z = 457.1 [M + H]^+$.



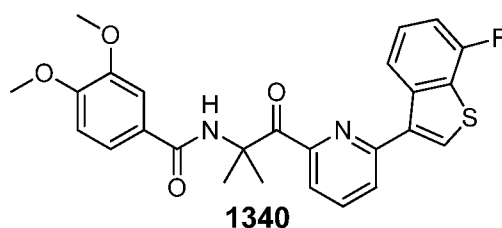
[0838] To a solution of crude **13-A9** (200mg, 0.9 mmol) in DME: H₂O=10:1 (2 mL) under N₂ was added Cs₂CO₃ (590 mg, 1.8 mmol), Pd(dppf)₂Cl₂ (20 mg, 0.027 mmol) and **12-C** (500 mg, 1.8 mmol). The mixture was heated to 85°C for 3 h (as monitored by TLC, PE: EA=1:3). After conversion, the mixture was filtered and purified by prep-HPLC to give compound **1337** (5 mg, 2.3 %). +ESI-MS: m/z = 467.1 [M + H]⁺.



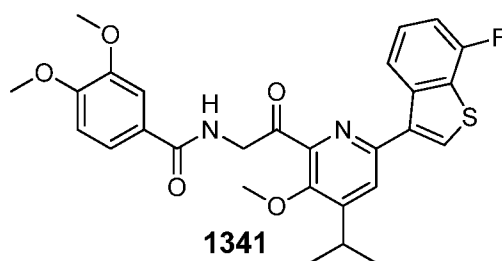
[0839] To a solution of crude **13-A10** (200mg, 0.44 mmol) in DME: H₂O=10:1 (5 mL) under N₂ was added Cs₂CO₃ (289 mg, 0.88 mmol), Pd (dppf)₂Cl₂ (9.6 mg, 0.013 mmol) and **12-C** (245 mg, 0.88 mmol). The mixture was heated to 85°C for 3 h (as monitored by TLC, PE:EA=1:3). After conversion, the mixture was filtered and purified by prep-HPLC to give compound **1338** (20 mg, 9.5 %). +ESI-MS: m/z = 481.1 [M + H]⁺.



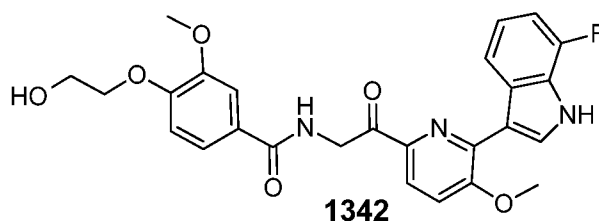
[0840] Compound **1339** was obtained following the procedure for obtaining compound **1300** by using 4-(3,4-dimethoxyphenyl)-N-methoxy-N-methyl-4-oxobutanamide and 2,6-dibromopyridine as the starting materials. Compound **1339** was obtained as a white solid. +ESI-MS: m/z = 450.1 [M + H]⁺.



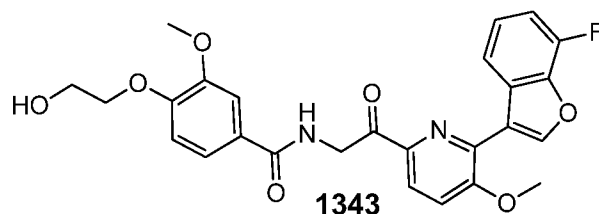
[0841] Compound **1340** was obtained following the procedure for obtaining compound **1300** by using methyl 2-amino-2-methylpropanoate and 2,6-dibromopyridine as the starting materials. Compound **1340** was obtained as a white solid. +ESI-MS: m/z 479.1 $[M + H]^+$.



[0842] Compound **1341** was obtained following the procedure for obtaining compound **1300** by using 2,6-diiodo-4-isopropyl-3-methoxypyridine as the starting material. Compound **1341** was obtained as a white solid. +ESI-MS: m/z 523.1 $[M + H]^+$.

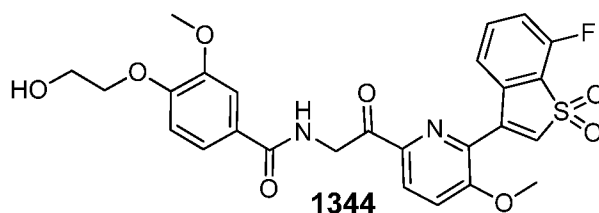


[0843] Compound **1342** was obtained following the procedure for obtaining compound **1325** by using 7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole as the starting material. Compound **1342** was obtained as a white solid. +ESI-MS: m/z 494.2; $[M + H]^+$.

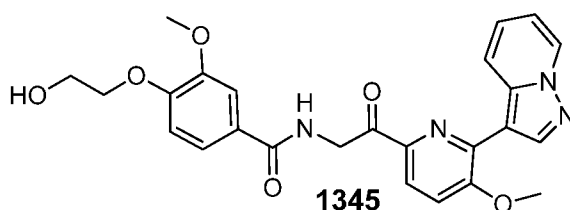


[0844] Compound **1343** was obtained following the procedure for obtaining compound **1325** by using 2-(7-fluorobenzofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-

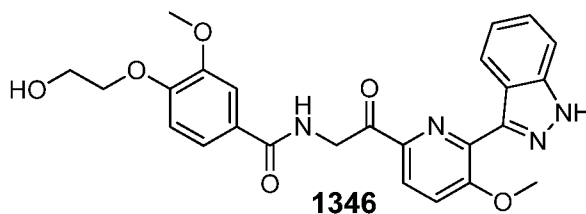
dioxaborolane as the starting material. Compound **1343** was obtained as a white solid. +ESI-MS: m/z 495.1 $[M + H]^+$.



[0845] Compound **1344** was obtained following the procedure for obtaining compound **1325** by using 7-fluoro-3-(tributylstannyl)benzo[b]thiophene 1,1-dioxide as the starting material. Compound **1344** was obtained as a white solid. +ESI-MS: m/z 543.1 $[M + H]^+$.

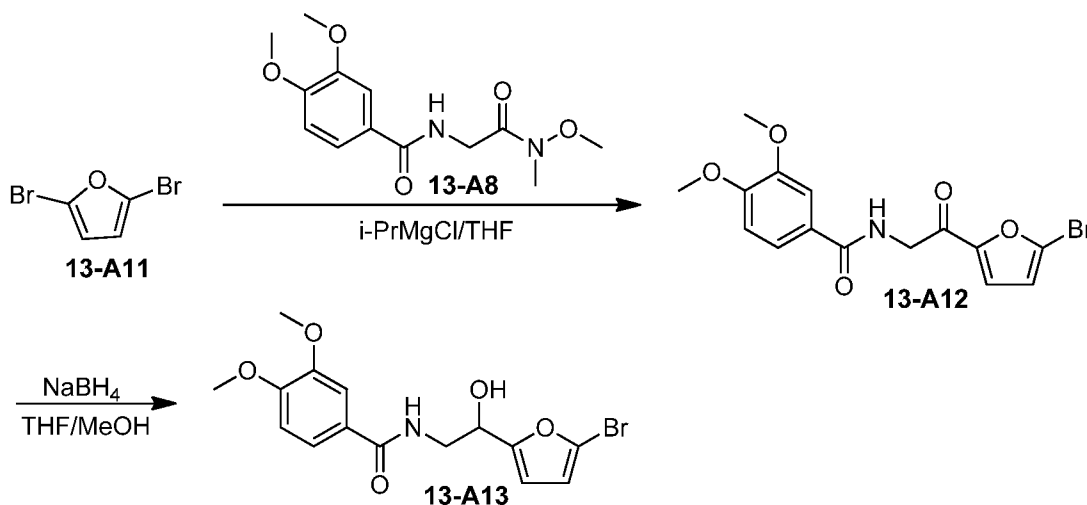


[0846] Compound **1345** was obtained following the procedure for obtaining compound **1325** by using 3-(trimethylstannyl)pyrazolo[1,5-a]pyridine as the starting material. Compound **1345** was obtained as a white solid. +ESI-MS: m/z 476.9 $[M + H]^+$.



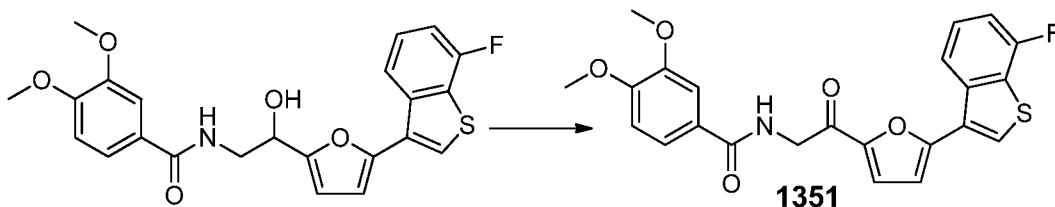
[0847] Compound **1346** was obtained following the procedure for obtaining compound **1325** by using 1-((2-(trimethylsilyl)ethoxy)methyl)-3-(trimethylstannyl)-1H-indazole as the starting material. Compound **1346** was obtained as a white solid. +ESI-MS: m/z 477.4 $[M + H]^+$.

EXAMPLE 13-10
Preparation of Compound 13-A13



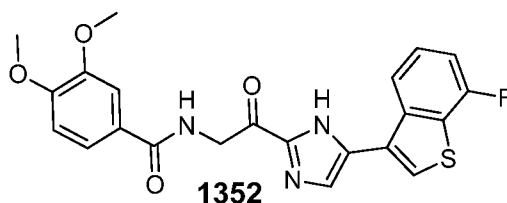
[0848] A 50 mL flask with a magnetic stirring bar was charged with **13-A11** (223 mg, 1.0 mmol), Weinreb amide (**13-A8**, 282 mg, 1.0 mmol), and THF (10 mL) under N₂ atmosphere. The solution was treated with *i*-PrMgCl (1.3 M, 2.0 eq.) dropwise at rt. The mixture was stirred for 1 h at rt. Water (50 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 MgSO₄ and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (PE) to provide **13-A12** as a solid (332 mg, 90%). +ESI-MS: *m/z* 367.0, 369.0 [M + H]⁺.

[0849] To a stirred solution of **13-A12** (368 mg, 1.0 mmol) in MeOH/THF (5 mL/5 mL) was added NaBH₄ (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 **13-A13** as a colorless oil (370 mg, 100%). +ESI-MS: *m/z* 369.0, 371.0 [M + H]⁺.

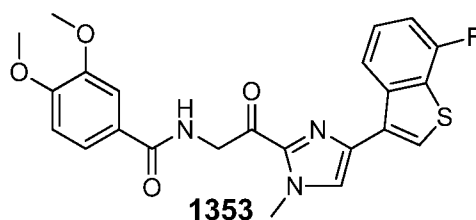


[0850] To a solution of N-(2-(5-(7-fluorobenzo[b]thiophen-3-yl)furan-2-yl)-2-hydroxyethyl)-3,4-dimethoxybenzamide (88 mg, 0.2 mmol) in CH₂Cl₂ (10 mL) was added DMP (170 mg, 0.4 mmol). The mixture was stirred at rt until the starting material was

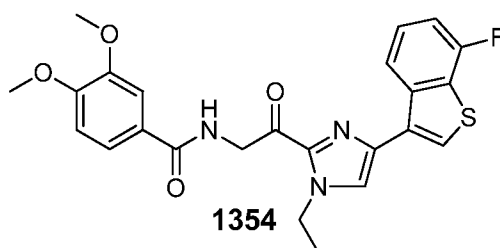
consumed. The mixture was concentrated at low pressure to give the crude product, which was purified by silica gel column chromatography (PE/EA) to give compound **1351** as a white solid (68 mg, 80%). +ESI-MS: m/z 439. 9 $[M + H]^+$.



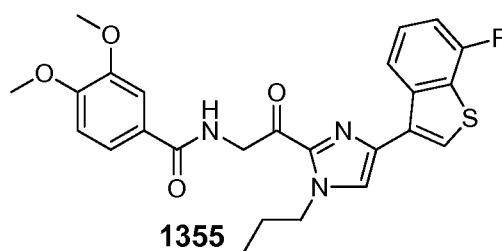
[0851] Compound **1352** was obtained following the procedure for obtaining compound **1351** by using 2,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1352** was obtained as a white solid. +ESI-MS: m/z 440. 0 $[M + H]^+$.



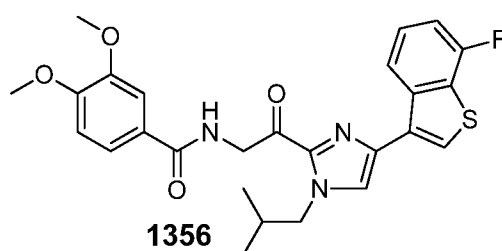
[0852] Compound **1353** was obtained following the procedure for obtaining compound **1351** by using 2,4-dibromo-1-methyl-1H-imidazole and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1353** was obtained as a white solid. +ESI-MS: m/z 453.8 $[M + H]^+$.



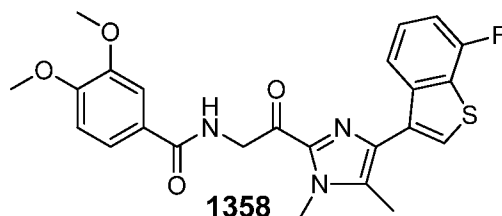
[0853] Compound **1354** was obtained following the procedure for obtaining compound **1351** by using 2,4-dibromo-1-ethyl-1H-imidazole and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1354** was obtained as a white solid. +ESI-MS: m/z 468.1 $[M + H]^+$.



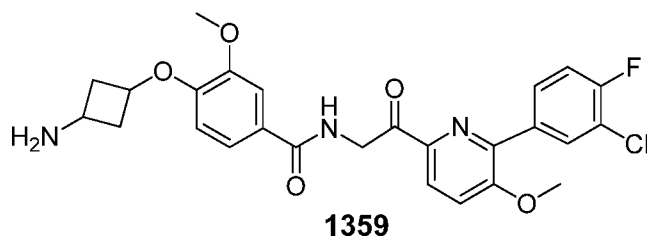
[0854] Compound **1355** was obtained following the procedure for obtaining compound **1351** by using 2,4-dibromo-1-propyl-1H-imidazole and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1355** was obtained as a white solid. +ESI-MS: m/z 482.5 $[M + H]^+$.



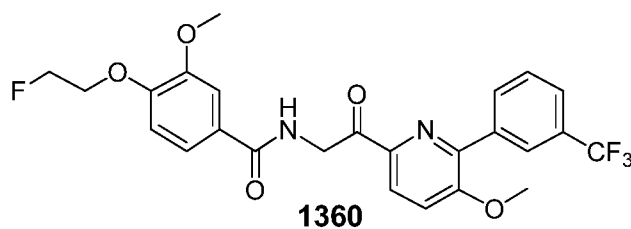
[0855] Compound **1356** was obtained following the procedure for obtaining compound **1351** by using 2,4-dibromo-1-isobutyl-1H-imidazole and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1356** was obtained as a white solid. +ESI-MS: m/z 496.1 $[M + H]^+$.



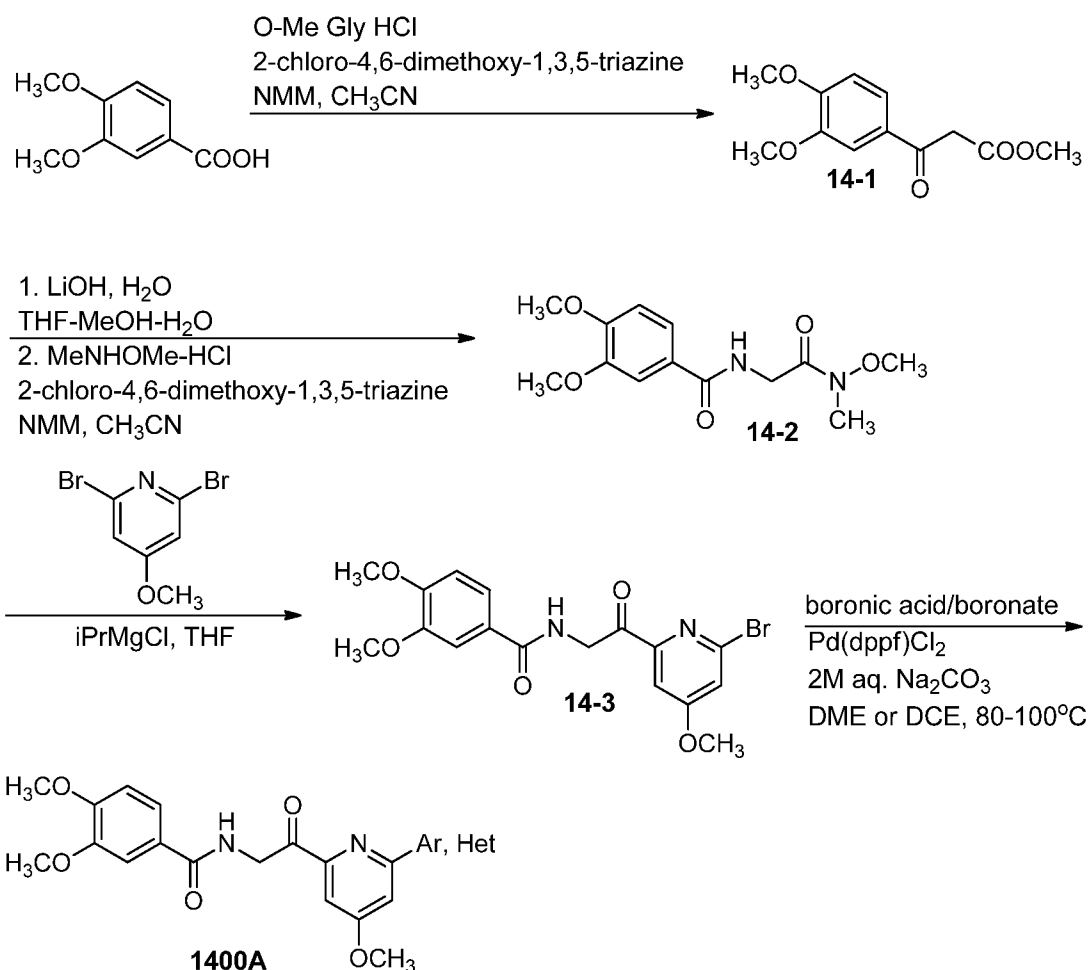
[0856] Compound **1358** was obtained following the procedure for obtaining compound **1351** by using 2,4-dibromo-1,5-dimethyl-1H-imidazole and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the starting materials. Compound **1358** was obtained as a white solid. +ESI-MS: m/z 467.8 $[M + H]^+$.



[0857] Compound **1359** was obtained following the procedure for obtaining compound **1310** by using 2-amino-1-(6-(3-chloro-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol and 4-(3-((tert-butoxycarbonyl) amino) cyclobutoxy)-3-methoxybenzoic acid as the starting materials. Compound **1359** was obtained as a white solid. +ESI-MS: m/z 513.9 $[M+H]^+$.



[0858] Compound **1360** was obtained following the procedure for obtaining compound **1325** by using **3-H** and (3-(trifluoromethyl)phenyl)boronic acid as the starting material. Compound **1360** was obtained as a white solid. +ESI-MS: m/z 505.2 $[M+H]^+$.

EXAMPLE 14-1**Preparation of General Compound 1400A**

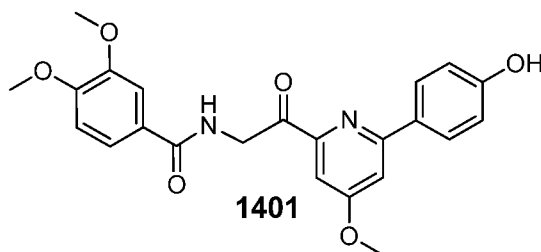
[0859] A mixture of 3,4-dimethoxybenzoic acid (15.0 g, 82.4 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (20.1 g, 115 mmol) and NMM (18.4 mL, 132 mmol) in CH₃CN (60 mL) was stirred at rt for 30 mins. Glycine methylester hydrochloride (12.4 g, 99.0 mmol) and NMM (10.9 mL, 99.0 mmol) were added and the reaction was stirred for 2 h. The volatiles were removed under reduced pressure. The residue was taken up with EtOAc and the organic portion was washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **14-1** (21.1 g) was used to the next step without further purification.

[0860] Monohydrate LiOH (11.0 g, 261 mmol) was added to **14-1** (21.1 g) dissolved in a 2:1:1 THF-MeOH-H₂O mixture (80 mL). The reaction was stirred at rt for 1 h. The organic solvents were removed under reduced pressure. The residue was taken up with

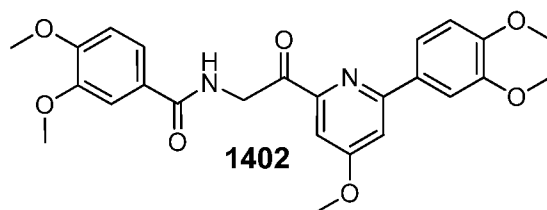
water and the aqueous portion was extracted twice with EtOAc. The combined organic portions were dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. The residue was dissolved in CH_3CN (60 mL) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (14.4 g, 107 mmol) and NMM (14.5 mL, 132 mmol) were added to the mixture. After 30 mins, *N,O*-dimethylhydroxylamine hydrochloride (10.4 g, 107 mmol) and NMM (11.7 mL, 107 mmol) were added. The mixture was stirred at rt for 2 h. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc, and the organic portion was washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **14-2** (9.5 g). UPLC/MS(ES^+), m/z : 283.10 $[\text{M}+\text{H}]^+$.

[0861] A 2M solution of *i*-PrMgCl in THF (3.0 mL, 6.04 mmol) was added to a solution of 2,6-dibromo-4-methoxypyridine (800 mg, 3.02 mmol) in dry THF (6 mL). The mixture was stirred at rt for 30 mins and added *via cannula* to a solution of **14-2** (500 mg, 1.77 mmol) in THF (5 mL), which had been pre-heated to 40 °C. The reaction was stirred at 40°C for 1 h, cooled down to rt and quenched with a 1M aq HCl solution. The organic portion was diluted with EtOAc, washed twice with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded the **14-3** as a white solid (200 mg, 27%). UPLC/MS(ES^+), m/z : 409.10 $[\text{M}+\text{H}]^+$.

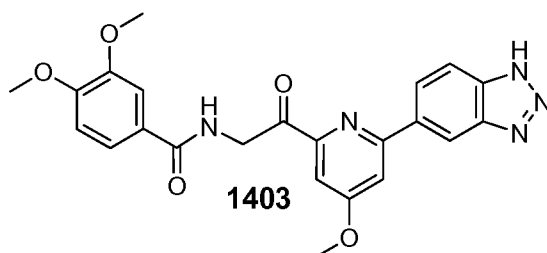
[0862] A mixture of **14-3** (170 mg, 0.390 mmol), boronic acid/ester (0.975 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (14.0 mg, 0.019 mmol) and aq Na_2CO_3 (2M solution, 585 μL , 1.17 mmol) in DME (7 mL) was degassed and heated to 85°C for 2 h (or until disappearing of the starting material). The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc) afforded compound **1400A**.



[0863] Compound **1401** was obtained by reacting **14-3** with (4-hydroxyphenyl)boronic acid according to the procedure shown in Example 14-1. Compound **1401** was obtained as a white solid (26%). UPLC/MS(ES^+), m/z : 423.18 $[\text{M}+\text{H}]^+$.

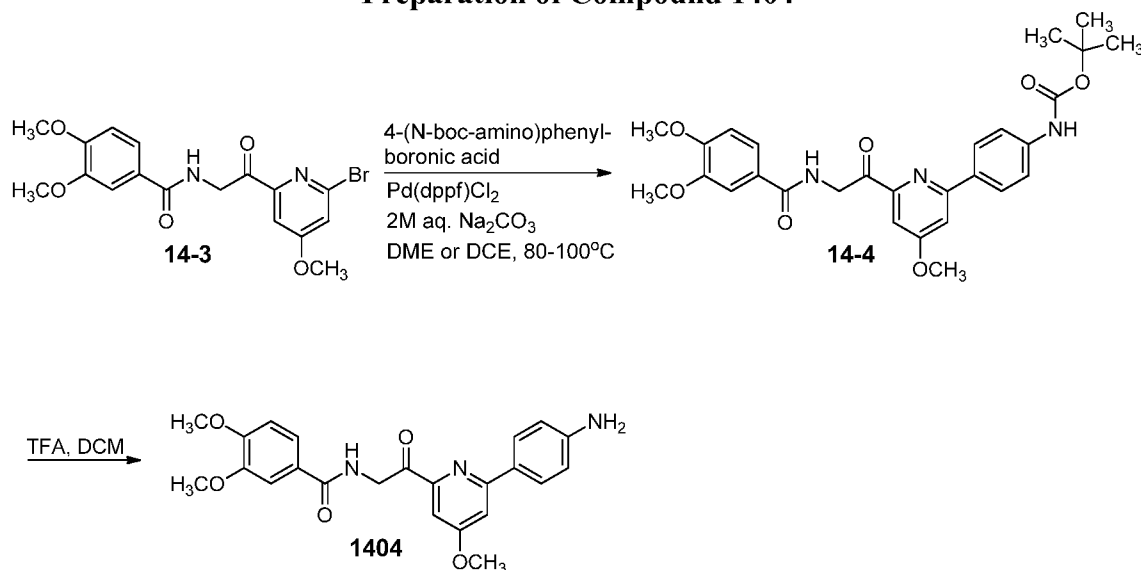


[0864] Compound **1402** was obtained by reacting **14-3** with 1,4-benzodioxane-6-boronic acid according to the procedure shown in Example 14-1. Compound **1402** was obtained as a grey solid (42%). UPLC/MS(ES^+), m/z : 465.20 $[\text{M}+\text{H}]^+$.



[0865] A mixture of **14-3** (100 mg, 0.240 mmol), 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triphenylmethyl)-1H-1,2,3-benzotriazole (233 mg, 0.480 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (26.0 mg, 0.036 mmol) and aq Na_2CO_3 (2M solution, 360 μL , 0.720 mmol) in DME (2 mL) was degassed and stirred. The mixture was heated to 80 $^\circ\text{C}$ for 48 h. Water and DCM were added. The mixture was filtered 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 3,4-dimethoxy-N-(2-{4-methoxy-6-[1-(triphenylmethyl)-1H-1,2,3-benzotriazol-5-yl]pyridin-2-yl}-2-oxoethyl)benzamide (90 mg, 54%). This compound was dissolved in DCM (3 mL) and treated with TFA (1 mL). The volatiles were removed under reduced pressure. The residue was purified by prep-HPLC to afford **1403** as an off white solid (8 mg, 14%). UPLC/MS(ES^+), m/z : 448.22 $[\text{M}+\text{H}]^+$.

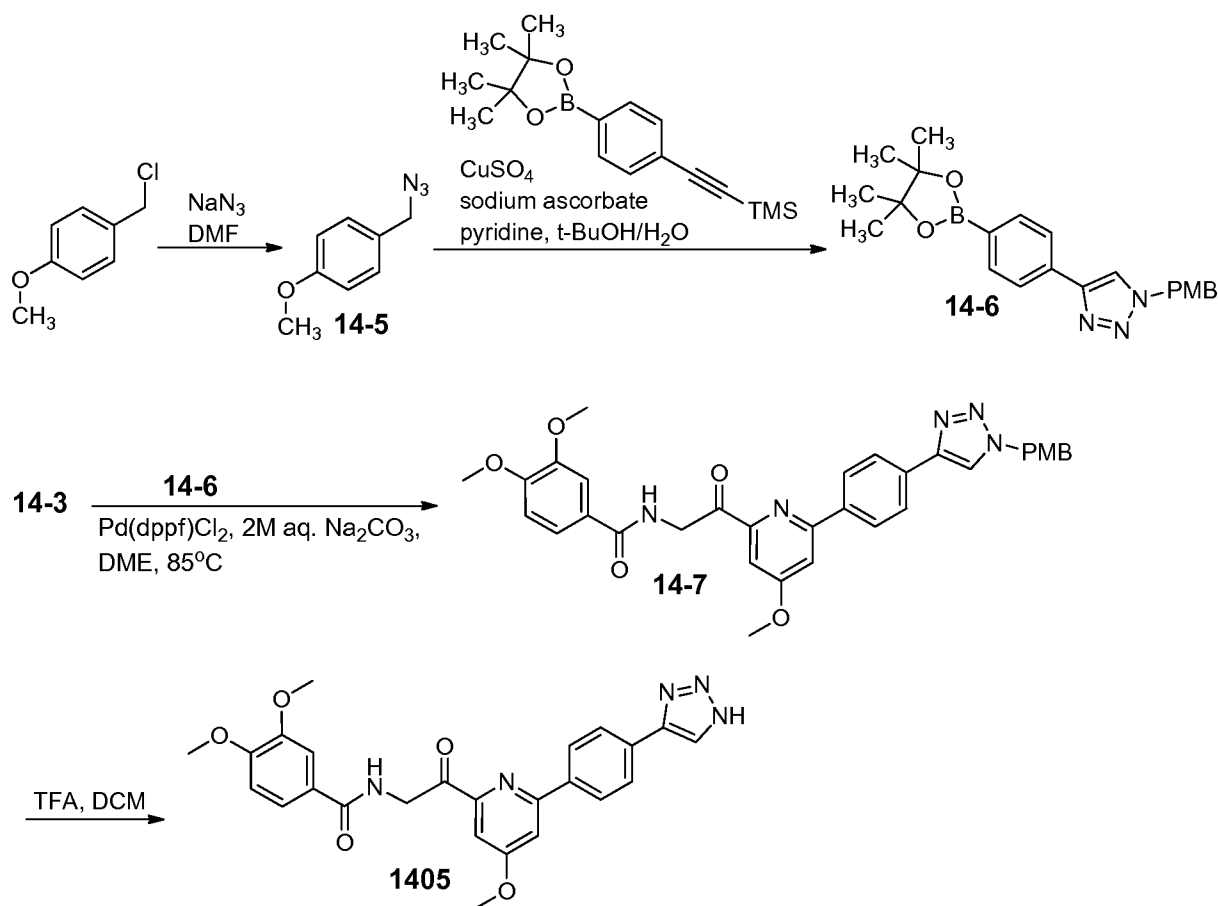
EXAMPLE 14-2
Preparation of Compound 1404



[0866] A mixture of **14-3** (130 mg, 0.320 mmol), 4-(N-boc-amino)phenylboronic acid (111 mg, 0.470 mmol), Pd(dppf)Cl₂ (33.0 mg, 0.047 mmol) and aq Na₂CO₃ (2M solution, 320 uL, 0.640 mmol) in DME (3.2 mL) was degassed and stirred at 85°C for 16 h. Water was added and the mixture was extracted twice with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered and concentrated in vacuo. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 30:70) afforded **14-4** as a grey solid (75 mg, 45%). UPLC/MS(ES⁺), m/z: 522.20 [M+H]⁺.

[0867] TFA (300 uL) was added to a mixture of **14-4** (75 mg, 0.026 mmol) in DCM (1 mL). After 1 h, the reaction was diluted with DCM and the organic portion was washed with a saturated aq NaHCO₃ solution, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford **1404** as a grey solid (11 mg, 18%). UPLC/MS(ES⁺), m/z: 422.15 [M+H]⁺.

EXAMPLE 14-3
Preparation of Compound 1405



[0868] Sodium azide (249 mg, 3.83 mmol) was added to a solution of 1-(chloromethyl)-4-methoxybenzene (500 mg, 3.19 mmol) in DMF (5 mL). The mixture was stirred at rt for 1 h. Et_2O was added and the organic portion was washed with a saturated aq NH_4Cl solution. The aqueous portion was back-extracted with Et_2O . The combined organic portions were dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure to afford **14-5** as a colorless oil (500 mg, 96%). ^1H NMR (400 MHz, CDCl_3) δ ppm 3.85 (s, 3 H), 4.30 (s, 2 H), 6.95 (d, $J=8.8$ Hz, 2 H), 7.28 (d, $J=8.8$ Hz, 2 H).

[0869] A mixture of **14-5** (500 mg, 3.06 mmol), trimethyl(2-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethynyl)silane (120 mg, 0.399 mmol), CuSO_4 (7.0 mg, 0.041 mmol), 0.1M aq sodium ascorbate solution (416 μL , 0.041 mmol) and pyridine (504 μL , 6.24 mmol) in a 2:1 $t\text{-BuOH}-\text{H}_2\text{O}$ mixture (3 mL) was stirred with heat at 60°C for 18 h. The volatiles were removed under reduced pressure. The residue was partitioned between

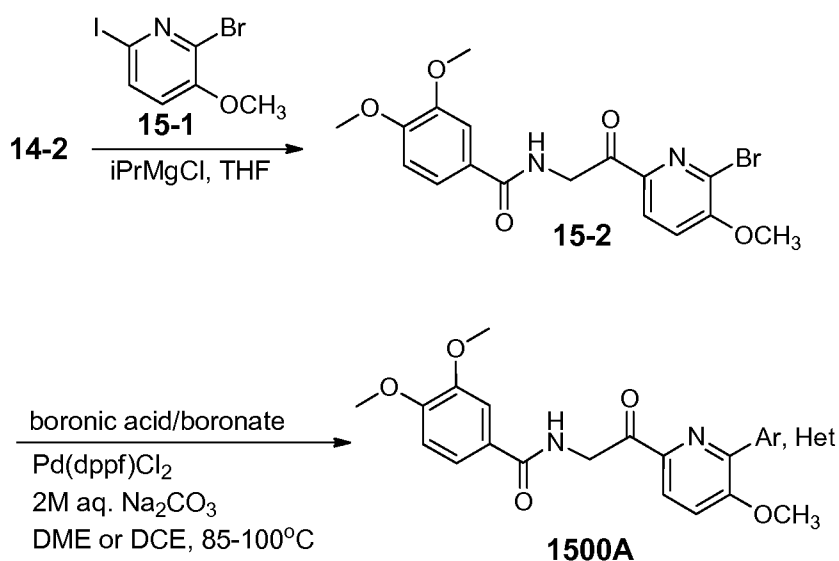
EtOAc and NH_4OH solution; the layers were separated and the aqueous phase was back-extracted with EtOAc. The combined organic portions were dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure to afford crude **14-6** (140 mg), which was used in the next step without further purification. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ ppm 1.96 (s, 12 H), 3.82 (s, 3 H), 5.59 (s, 2 H), 6.97 (d, $J=8.5$ Hz, 2 H), 7.37 (d, $J=8.5$ Hz, 2 H), 7.71 (d, 1 H), 7.78-7.84 (m, 3 H), 8.32 (d, $J=10.3$ Hz, 1 H).

[0870] A mixture of **14-3** (106 mg, 0.259 mmol), **14-6** (140 mg, 0.358 mmol), Pd(dppf)Cl_2 (28.4 mg, 0.038 mmol) and aq Na_2CO_3 (2M solution, 323 μL , 0.646 mmol) in DME (5 mL) was degassed and stirred with heat to 85°C for 50 min. After cooling to rt, the mixture was diluted with water and extracted 3 times with EtOAc. The combined organic portions were dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **14-7** as a white solid (43 mg, 28%). UPLC/MS(ES^+), m/z : 594.20 [MH^+].

[0871] Compound **14-7** was dissolved in TFA (5 mL), and the solution was heated to 65°C . After 48 h, the mixture was cooled to rt and diluted with EtOAc. The organic portion was washed with a 2M aq Na_2CO_3 solution, dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **1405** as a light yellow solid (10 mg, 29%). UPLC/MS(ES^+), m/z : 474.20 [$\text{M}+\text{H}^+$].

EXAMPLE 15-1

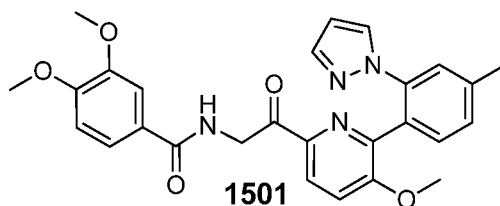
Preparation of General Compound 1500A



[0872] Isopropylmagnesium chloride (2M solution in THF, 22.0 mL, 44.0 mmol) was added dropwise to a solution of **15-1** (8.30 g, 13.2 mmol) and **14-2** (5.00 g, 8.80 mmol) in dry THF (60 mL). The reaction was stirred at rt for 30 mins. A 1M aq HCl solution was added and the mixture was extracted with EtOAc. The organic portion was dried (Na₂SO₄) filtered and evaporated under reduced pressure. Trituration of the residue with a 1:1 DCM-MeOH mixture **15-2** as an off white solid (3.80 g, 53%). ¹H NMR (400 MHz, CDCl₃) δ ppm 3.97 (s, 3 H), 3.99 (s, 3 H), 4.05 (s, 3 H), 5.14 (d, *J*=4.5 Hz, 2 H), 6.94 (d, *J*=8.3 Hz, 1 H), 7.03 (br. s., 1 H), 7.27 (d, *J*=8.5 Hz, 1 H), 7.46 (dd, *J*=8.3, 2.0 Hz, 1 H), 7.52 (d, *J*=2.0 Hz, 1 H), 8.10 (d, *J*=8.3 Hz, 1 H).

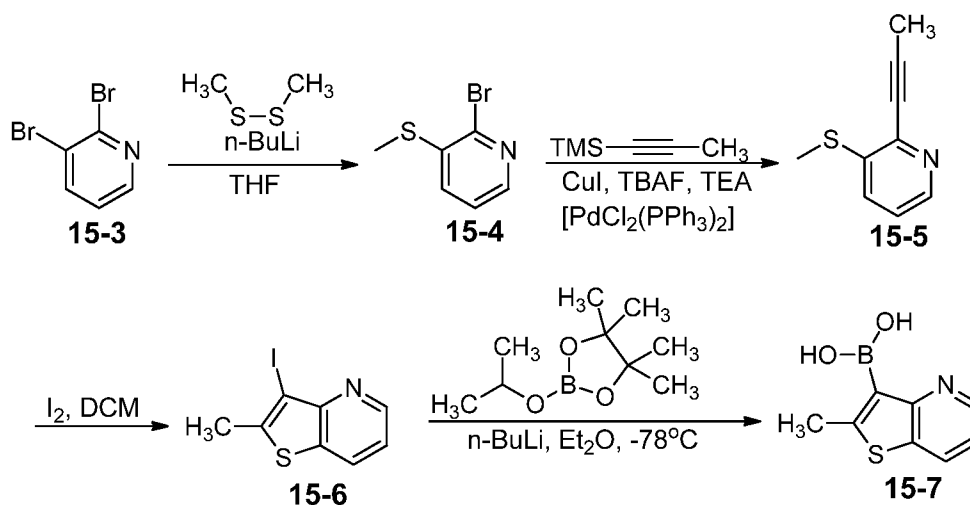
[0873] General Procedure A (1500A): A mixture of **15-2** (0.390 mmol), boronic acid/ester (0.975 mmol), Pd(dppf)Cl₂ (0.019 mmol) and aq Na₂CO₃ (2M solution, 1.17 mmol) in DME (7 mL) was degassed and heated to 85°C for 2 h (or until disappearing of the starting material). The volatiles were removed under reduced pressure. Chromatography of the residue afforded compound **1500A**.

[0874] General Procedure B (1500A): A mixture of N-(2-(6-bromo-5-methoxypyridin-2-yl)-2-oxoethyl)-3,4-dimethoxybenzamide (**B-2**, 0.245 mmol), KF (0.980 mmol), Pd(dppf)Cl₂ (0.025 mmol) and boronic acid/boronate (0.370 mmol) in dry DMF (1 mL) was heated to 85°C. When complete (TLC or UPLC monitoring), the mixture was cooled to rt, diluted with EtOAc and washed with water and brine. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue afforded compound **1500A**.



[0875] Compound **1501** was obtained by reacting **15-2** with [4-methyl-2-(1H-pyrazol-1-yl)phenyl]boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1501** was obtained as a pale yellow solid (18%). UPLC/MS(ES⁺), *m/z*: 487.20 [M+H]⁺.

EXAMPLE 15-2
Preparation of Compound 15-7



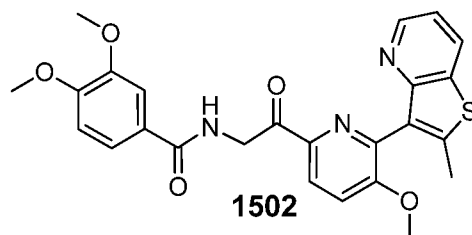
[0876] *n*-Butyllithium (1.6 M solution in hexane, 6.5 mL, 10.5 mmol) was added to a solution of 2,3-dibromopyridine (**15-3**, 2.50 g, 10.8 mmol) in dry THF (45 mL), which was pre-cooled to -78°C . After 1 h, dimethyl disulfide (2.25 mL, 21.5 mmol) was added and the mixture was stirred for an additional 1 h. The mixture was allowed to reach rt. Water was added and the aqueous portion was extracted twice with EtOAc. The combined organic portions were washed with water, dried (Na_2SO_4) filtered and evaporated. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) **15-4** as a brown oil (670 mg, 30%). ^1H NMR (CDCl_3) δ : 2.45-2.57 (m, 3H), 7.24-7.30 (m, 1H), 7.41 (dd, $J=7.9, 1.4$ Hz, 1H), 8.15 (dd, $J=4.5, 1.5$ Hz, 1H).

[0877] To a mixture of **15-4** (1.2 g, 5.9 mmol), 1-(trimethylsilyl)propyne (662 mg, 5.90 mmol) and copper(I) iodide (55.0 mg, 0.290 mmol) in TEA (37.5 mL) was added tetrabutylammonium fluoride (1M solution in THF, 17.9 mL). The mixture was degassed for 30 mins. Bis(triphenylphosphine)palladium(II) dichloride (203 mg, 0.290 mmol) was added and the mixture was stirred at 40°C under argon overnight. EtOAc was added and the organic portion was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) afforded **15-5** as a yellow oil (200 mg, 20%). ^1H NMR (CDCl_3) δ : 2.08-2.25 (m, 3H), 2.49 (s, 3H), 7.19 (dd, $J=8.2, 4.6$ Hz, 1H), 7.45 (dd, $J=8.0, 1.0$ Hz, 1H), 8.31 (d, $J=3.8$ Hz, 1H).

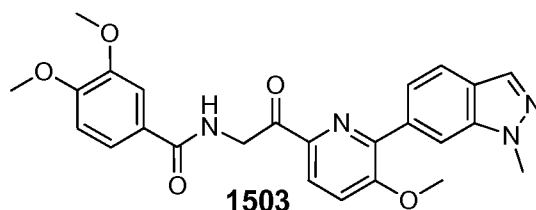
[0878] Iodine (464 mg, 1.83 mmol) dissolved in DCM (12.5 mL) was added dropwise to a solution of **15-5** (200 mg, 1.22 mmol) in DCM (12.5 mL). The mixture was

stirred at rt for 1 h, diluted with DCM and washed with water. The organic portion were dried (Na_2SO_4) filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) afforded **15-6** as a yellow solid (210 mg, 62%). ^1H NMR (CDCl_3) δ : 2.70 (s, 3H), 7.25-7.28 (m, 1H), 8.06 (dd, $J=8.0, 1.3$ Hz, 1H), 8.76 (dd, $J=4.5, 1.3$ Hz, 1H).

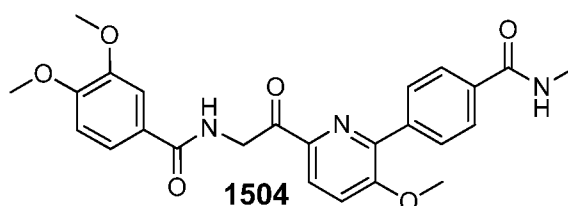
[0879] *n*-Butyllithium (1.6M solution in hexane, 489 μL , 0.790 mmol) was added dropwise to a solution of **15-6** (210 mg, 0.760 mmol) in dry Et_2O (4 mL), which had been pre-cooled to -78°C . The mixture was stirred at -78°C for 1 h. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (162 μL , 0.790 mmol) was added and the mixture was left to stir at -78°C overnight. The mixture was allowed to reach rt and water was added. The aqueous portion was extracted twice with EtOAc. The combined organic portions were dried (Na_2SO_4) filtered and evaporated. The residue was purified by reverse phase chromatography (water- CH_3CN , 100:0-0:100) to give **15-7** as a white solid (48 mg, 31%). UPLC/MS(ES^+), m/z : 193.99 $[\text{M}+\text{H}]^+$.



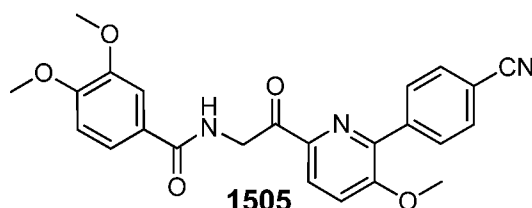
[0880] Compound **1502** was obtained by reacting **15-2** with **15-7** according to the procedure shown in Example 15-1, General Procedure A. Compound **1502** was obtained as an off-white solid (50%). UPLC/MS(ES^+), m/z : 478.15 $[\text{M}+\text{H}]^+$.



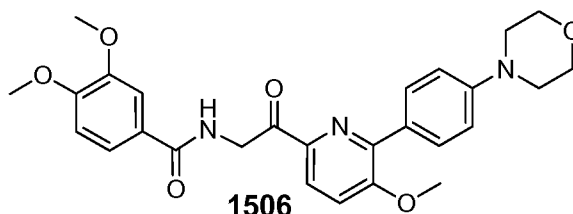
[0881] Compound **1503** was obtained by reacting **15-2** with 1-methyl-1H-indazole-6-boric acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1503** was obtained as a pale yellow solid (53%). UPLC/MS(ES^+), m/z : 461.18 $[\text{M}+\text{H}]^+$.



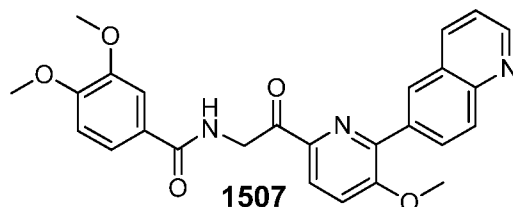
[0882] Compound **1504** was obtained by reacting **15-2** with [4-(methylcarbamoyl)phenyl]boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1504** was obtained as a pale yellow solid (7%). UPLC/MS(ES^+), m/z : 464.17 $[\text{M}+\text{H}]^+$.



[0883] Compound **1505** was obtained by reacting **15-2** with [(4-cyanophenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1505** was obtained as an off-white solid (48%). UPLC/MS(ES^+), m/z : 432.15 $[\text{M}+\text{H}]^+$.

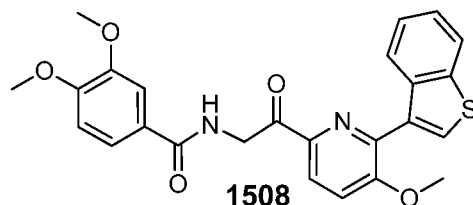


[0884] Compound **1506** was obtained by reacting **15-2** with 4-morpholine-phenyl-boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1506** was obtained as a light yellow solid (83%). UPLC/MS(ES^+), m/z : 492.19 $[\text{M}+\text{H}]^+$.

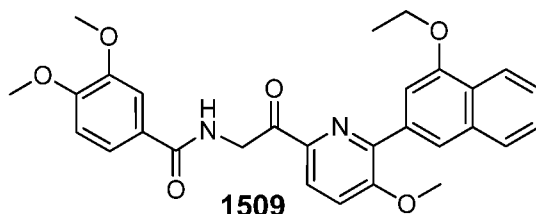


[0885] Compound **1507** was obtained by reacting **15-2** with (quinolin-6-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A.

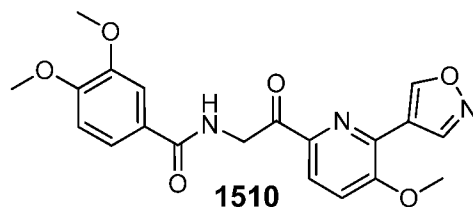
Compound **1507** was obtained as a yellow solid (62%). UPLC/MS(ES^+), m/z : 458.20 $[\text{M}+\text{H}]^+$.



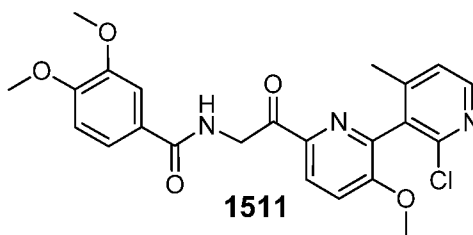
[0886] Compound **1508** was obtained by reacting **15-2** with (1-benzothiophen-3-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1508** was obtained as an off-white solid (59%). UPLC/MS(ES^+), m/z : 463.13 $[\text{M}+\text{H}]^+$.



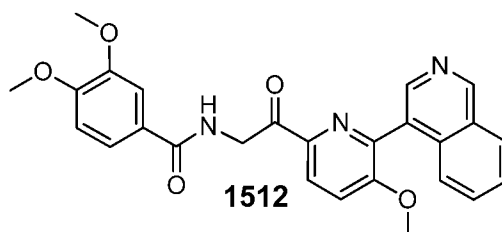
[0887] Compound **1509** was obtained by reacting **15-2** with (3-ethoxynaphthalen-1-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1509** was obtained as an off-white solid (31%). UPLC/MS(ES^+), m/z : 501.20 $[\text{M}+\text{H}]^+$.



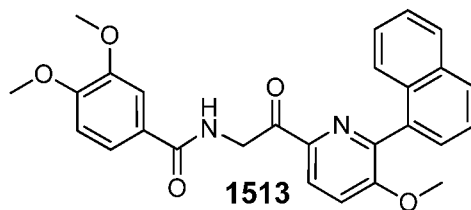
[0888] Compound **1510** was obtained by reacting **15-2** with (1,2-oxazol-4-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1510** was obtained as a white solid (43%). UPLC/MS(ES^+), m/z : 398.09 $[\text{M}+\text{H}]^+$.



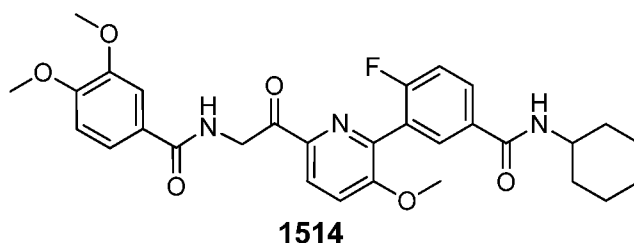
[0889] Compound **1511** was obtained by reacting **15-2** with (2-chloro-4-methylpyridin-3-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1511** was obtained as a pale yellow solid (19%). UPLC/MS(ES^+), m/z : 456.14 $[\text{M}+\text{H}]^+$.



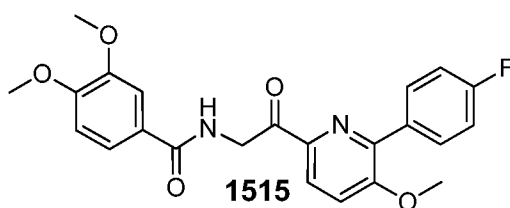
[0890] Compound **1512** was obtained by reacting **15-2** with (isoquinolin-4-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1512** was obtained as an off-white solid (38%). UPLC/MS(ES^+), m/z : 458.17 $[\text{M}+\text{H}]^+$.



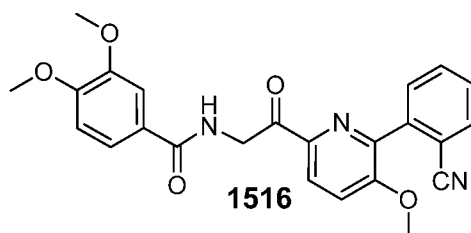
[0891] Compound **1513** was obtained by reacting **15-2** with (naphthalen-1-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1513** was obtained as a white solid (38%). UPLC/MS(ES^+), m/z : 457.17 $[\text{M}+\text{H}]^+$.



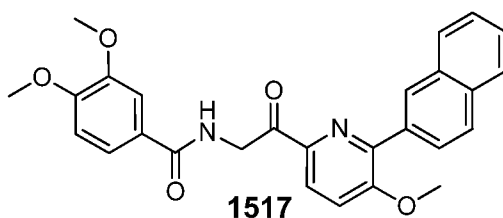
[0892] Compound **1514** was obtained by reacting **15-2** with [5-(cyclohexylcarbamoyl)-2-fluorophenyl]boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1514** was obtained as a pale yellow solid (45%). UPLC/MS(ES^+), m/z : 550.21 $[\text{M}+\text{H}]^+$.



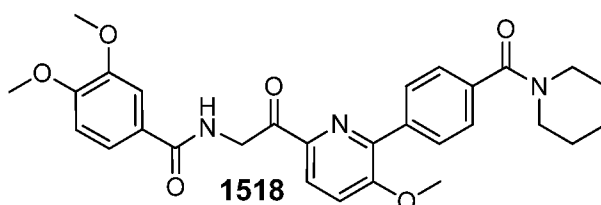
[0893] Compound **1515** was obtained by reacting **15-2** with (4-fluorophenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1515** was obtained as a pale yellow solid (79%). UPLC/MS(ES^+), m/z : 425.16 $[\text{M}+\text{H}]^+$.



[0894] Compound **1516** was obtained by reacting **15-2** with (2-cyanophenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1516** was obtained as a white solid (36%). UPLC/MS(ES^+), m/z : 432.16 $[\text{M}+\text{H}]^+$.

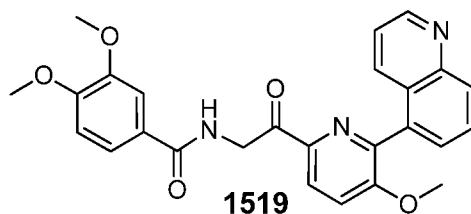


[0895] Compound **1517** was obtained by reacting **15-2** with (naphthalen-2-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1517** was obtained as a white solid (53%). UPLC/MS(ES^+), m/z : 457.16 $[\text{M}+\text{H}]^+$.

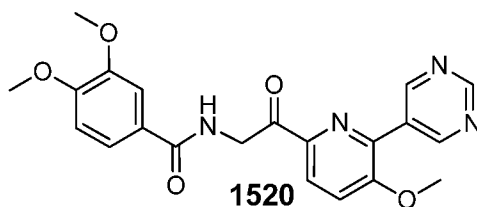


[0896] Compound **1518** was obtained by reacting **15-2** with {4-[(piperidin-1-yl)carbonyl]phenyl}boronic acid according to the procedure shown in Example 15-1,

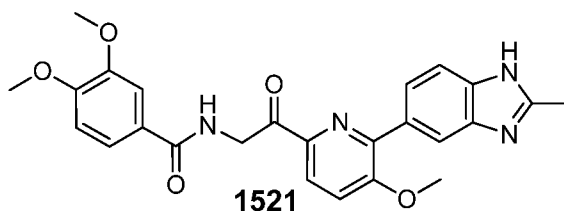
General Procedure A. Compound **1518** was obtained as an off-white solid (79%). UPLC/MS(ES^+), m/z : 518.20 $[\text{M}+\text{H}]^+$.



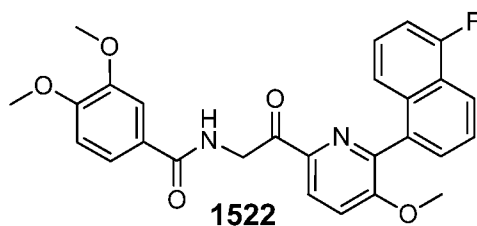
[0897] Compound **1519** was obtained by reacting **15-2** with (quinolin-5-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1519** was obtained as an off-white solid (53%). UPLC/MS(ES^+), m/z : 458.20 $[\text{M}+\text{H}]^+$.



[0898] Compound **1520** was obtained by reacting **15-2** with pyrimidine-5-boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1520** was obtained as a yellow solid (45%). UPLC/MS(ES^+), m/z : 409.16 $[\text{M}+\text{H}]^+$.

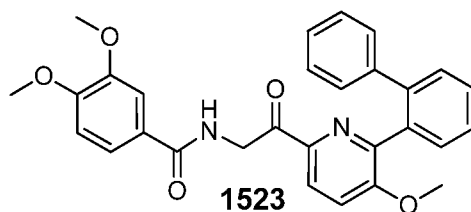


[0899] Compound **1521** was obtained by reacting **15-2** with 2-methyl-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole according to the procedure shown in Example 15-1, General Procedure A. Compound **1521** was obtained as a yellow solid (15%). UPLC/MS(ES^+), m/z : 461.17 $[\text{M}+\text{H}]^+$.

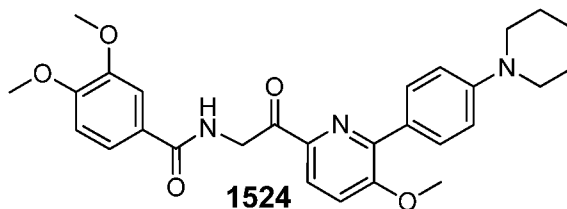


[0900] Compound **1522** was obtained by reacting **15-2** with 2-(5-fluoronaphthalen-1-yl)-5,5-dimethyl-1,3,2-dioxaborinane according to the procedure shown in Example 15-1, General Procedure A. Compound **1522** was obtained as a light pink solid (80%). UPLC/MS(ES^+), m/z : 475.15 $[\text{M}+\text{H}]^+$.

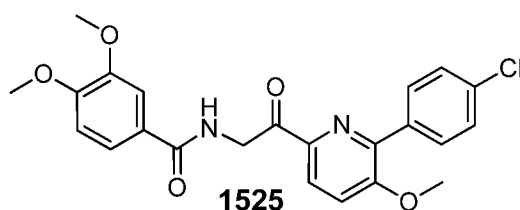
[0901] 2-(5-fluoronaphthalen-1-yl)-5,5-dimethyl-1,3,2-dioxaborinane: A mixture of 1-bromo-5-fluoronaphthalene (350 mg, 1.55 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (700 mg, 3.10 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (56.0 mg, 0.077 mmol) and KOAc (608 mg, 6.20 mmol) in DMF (4.5 mL) was degassed and heated to 85°C for 50 mins. After cooling to rt, water was added and the mixture was extracted with DCM. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) afforded the title compound as a white solid (320 mg, 80%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.12 (s, 6 H), 3.91 (s, 4 H), 7.15 (dd, $J=10.4$, 7.6 Hz, 1 H), 7.44 (td, $J=8.1$, 6.1 Hz, 1 H), 7.55 (dd, $J=8.2$, 7.1 Hz, 1 H), 8.12 (d, $J=6.5$ Hz, 1 H), 8.23 (d, $J=8.3$ Hz, 1 H), 8.58 (d, $J=8.5$ Hz, 1 H).



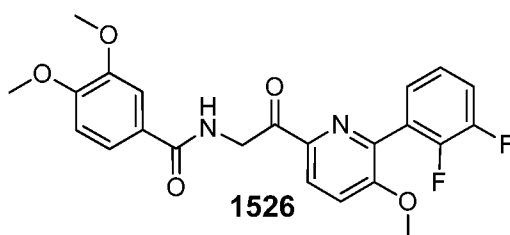
[0902] Compound **1523** was obtained by reacting **15-2** with 2-biphenylboronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1523** was obtained as an off-white solid (77%). UPLC/MS(ES^+), m/z : 483.19 $[\text{M}+\text{H}]^+$.



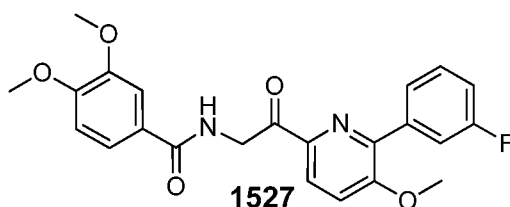
[0903] Compound **1524** was obtained by reacting **15-2** with [4-(piperidin-1-yl)phenyl]boronic acid hydrochloride according to the procedure shown in Example 15-1, General Procedure A. Compound **1524** was obtained as a yellow solid (84%). UPLC/MS(ES^+), m/z : 490.22 $[\text{M}+\text{H}]^+$.



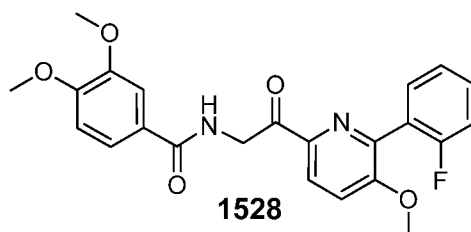
[0904] Compound **1525** was obtained by reacting **15-2** with (4-chlorophenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1525** was obtained as an off-white solid (83%). UPLC/MS(ES^+), m/z : 441.13 $[\text{M}+\text{H}]^+$.



[0905] Compound **1526** was obtained by reacting **15-2** with (2,3-difluorophenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1526** was obtained as an off-white solid (69%). UPLC/MS(ES^+), m/z : 443.13 $[\text{M}+\text{H}]^+$.

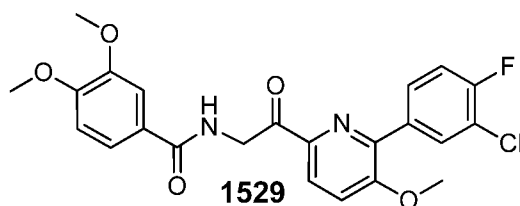


[0906] Compound **1527** was obtained by reacting **15-2** with (3-fluorophenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1527** was obtained as a white solid (72%). UPLC/MS(ES^+), m/z : 425.17 $[\text{M}+\text{H}]^+$.

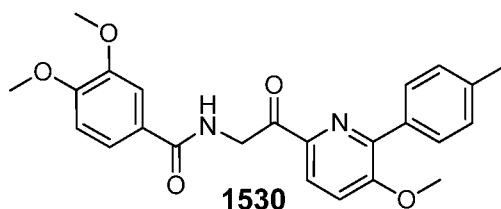


[0907] Compound **1528** was obtained by reacting **15-2** with (2-fluorophenyl)boronic acid according to the procedure shown in Example 15-1, General

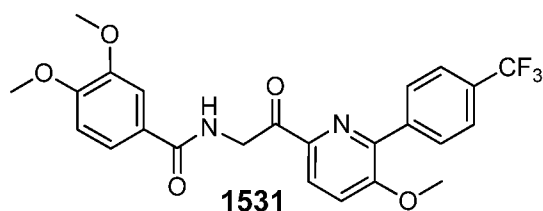
Procedure A. Compound **1528** was obtained as a white solid (56%). UPLC/MS(ES^+), m/z : 425.15 $[\text{M}+\text{H}]^+$.



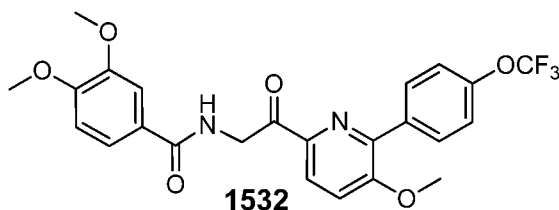
[0908] Compound **1529** was obtained by reacting **15-2** with (3-chloro-4-fluorophenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1529** was obtained as a light yellow solid (87%). UPLC/MS(ES^+), m/z : 459.11 $[\text{M}+\text{H}]^+$.



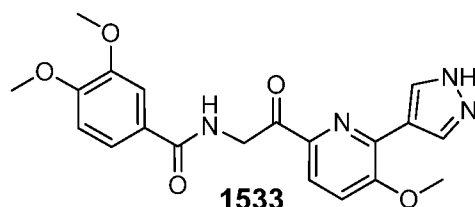
[0909] Compound **1530** was obtained by reacting **15-2** with (4-methylphenyl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1530** was obtained as a light orange solid (72%). UPLC/MS(ES^+), m/z : 421.17 $[\text{M}+\text{H}]^+$.



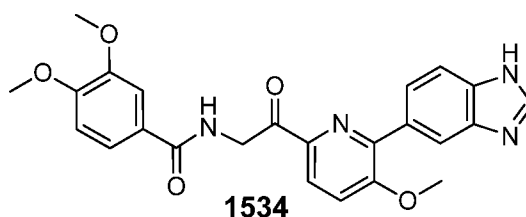
[0910] Compound **1531** was obtained by reacting **15-2** with [4-(trifluoromethyl)phenyl]boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1531** was obtained as a white solid (79%). UPLC/MS(ES^+), m/z : 475.12 $[\text{M}+\text{H}]^+$.



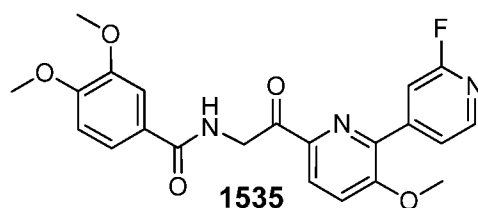
[0911] Compound **1532** was obtained by reacting **15-2** with [4-(trifluoromethoxy)phenyl]boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1532** was obtained as a white solid (72%). UPLC/MS(ES^+), m/z : 491.13 $[\text{M}+\text{H}]^+$.



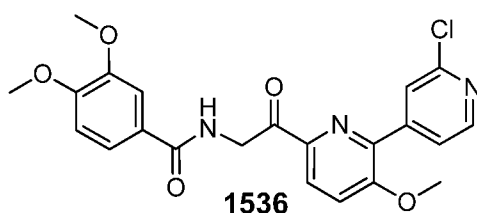
[0912] Compound **1533** was obtained by reacting **15-2** with (1H-pyrazol-4-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1533** was obtained as a light yellow solid (55%). UPLC/MS(ES^+), m/z : 397.15 $[\text{M}+\text{H}]^+$.



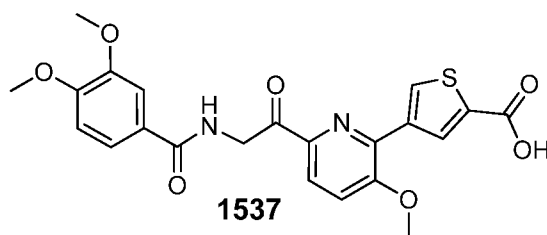
[0913] Compound **1534** was obtained by reacting **15-2** with (1H-1,3-benzodiazol-5-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. Compound **1534** was obtained as a light yellow solid (34%). UPLC/MS(ES^+), m/z : 447.20 $[\text{M}+\text{H}]^+$.



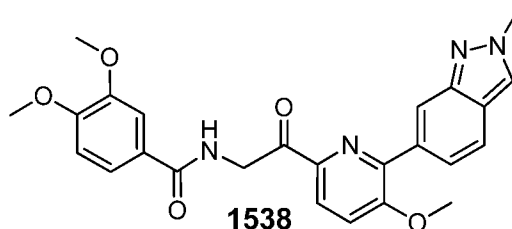
[0914] Compound **1535** (75%). was obtained by reacting **15-2** with (2-fluoropyridin-4-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. UPLC/MS(ES^+), m/z : 426.16 $[\text{M}+\text{H}]^+$.



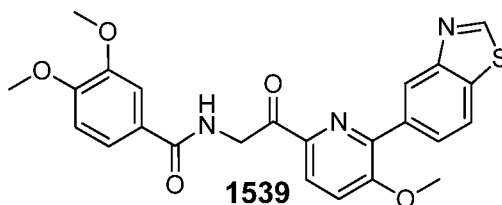
[0915] Compound **1536** (61%) was obtained by reacting **15-2** with (2-chloropyridin-4-yl)boronic acid according to the procedure shown in Example 15-1, General Procedure A. UPLC/MS(ES^+), m/z : 442.10 $[\text{M}+\text{H}]^+$.



[0916] Compound **1537** was obtained by reacting **15-2** with 4-(dihydroxyboranyl)thiophene-2-carboxylic acid according to the procedure shown in Example 15-1, General Procedure B. Compound **1537** was obtained as an off-white solid (7%). UPLC/MS(ES^+), m/z : 457.10 $[\text{M}+\text{H}]^+$.

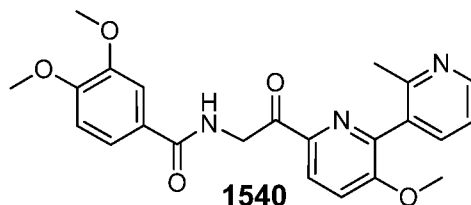


[0917] Compound **1538** was obtained by reacting **15-2** with 2-methyl-2H-indazol-6-yl-6-boronic acid according to the procedure shown in Example 15-1, General Procedure B. Compound **1538** was obtained as an off-white solid (21%). UPLC/MS(ES^+), m/z : 461.20 $[\text{M}+\text{H}]^+$.



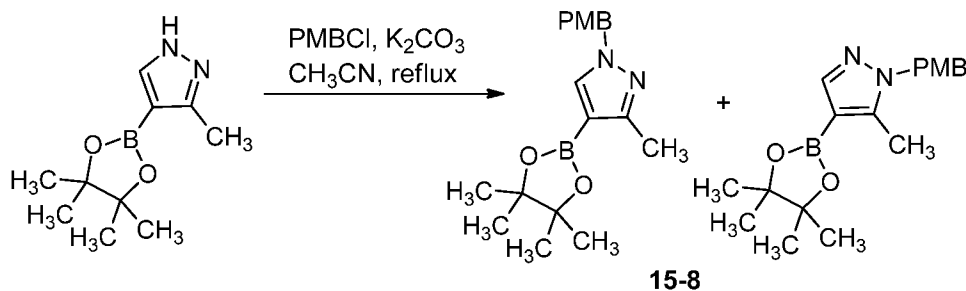
[0918] Compound **1539** was obtained by reacting **15-2** with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole according to the procedure shown in

Example 15-1, General Procedure B. Compound **1539** was obtained as an off-white solid (37%). UPLC/MS(ES⁺), m/z: 464.10 [M+H]⁺.

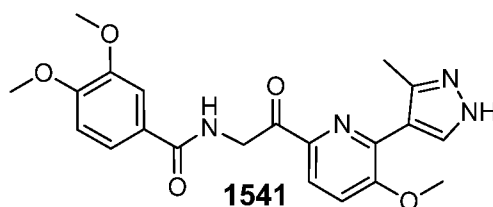


[0919] Compound **1540** was obtained by reacting **15-2** with 2-methylpyridin-3-yl-3-boronic acid according to the procedure shown in Example 15-1, General Procedure B. Compound **1540** was obtained as a pale yellow solid (46%). UPLC/MS(ES⁺), m/z: 422.20 [M+H]⁺.

EXAMPLE 15-3 **Preparation of Compound 15-8**



[0920] A mixture of 3-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (252 mg, 1.21 mmol), 1-(chloromethyl)-4-methoxybenzene (230 mg, 1.21 mmol) and K₂CO₃ (167 mg, 1.21 mmol) in CH₃CN (3 mL) was stirred with heat to reflux for 5 h. After cooling to rt, the mixture was filtered and the organic portion was concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) **15-8** as a mixture of regioisomers (320 mg, 80%). UPLC/MS(ES⁺), m/z: 329.17 [M+H]⁺.

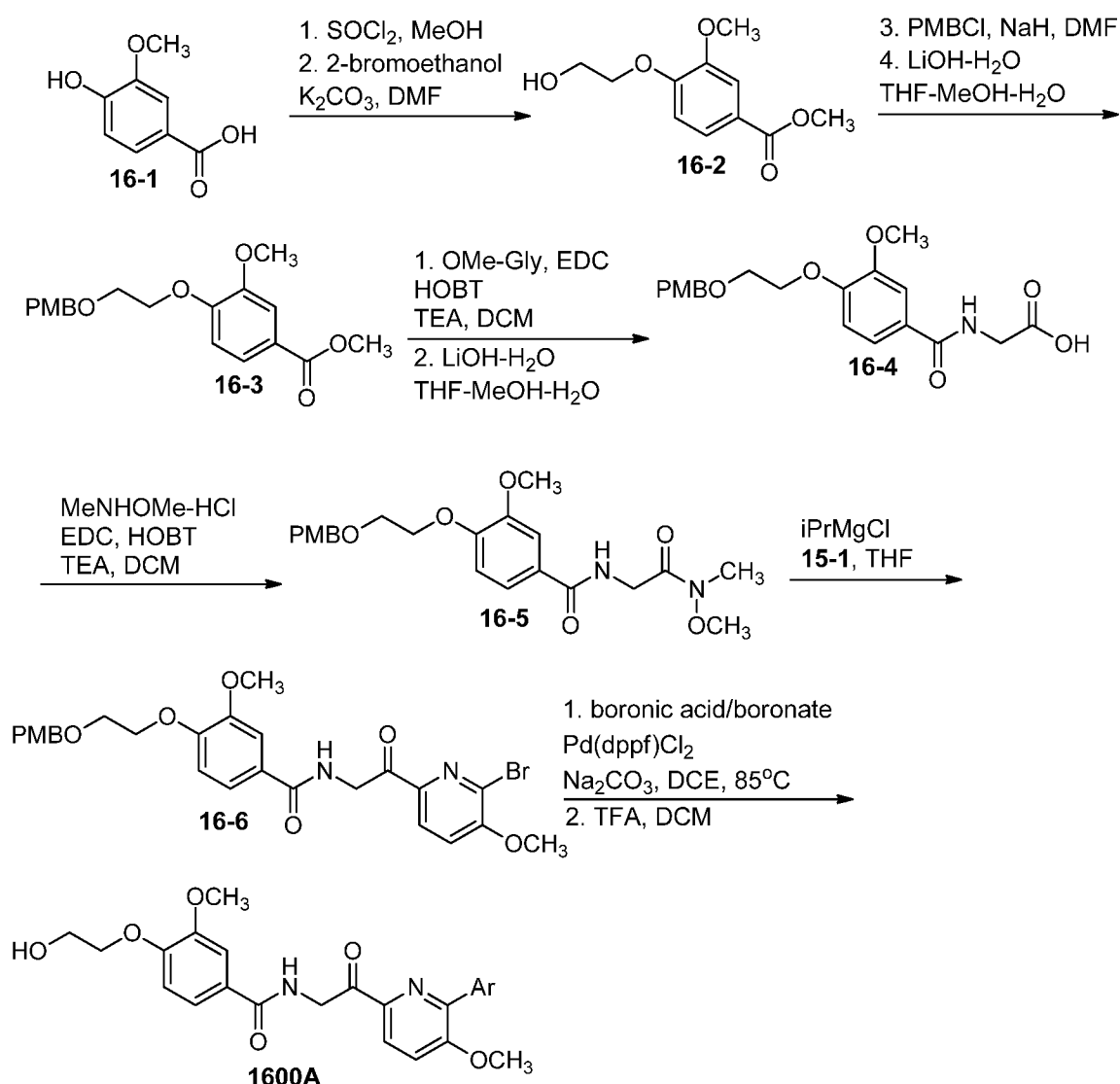


[0921] A mixture of **15-8** (250 mg, 0.761 mmol), **15-2** (124 mg, 0.300 mmol), Pd(Ph₃)₄ (51.0 mg, 0.150 mmol) and aq NaHCO₃ (2M solution, 450 uL, 0.900 mmol) in DME (2.5 mL) was heated to 120 °C under mw irradiation. After 30 mins, the mixture was

diluted with EtOAc and washed with brine. The organic portion was dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure. The residue was dissolved in TFA and the solution was heated to 65°C for 2 h. After cooling to rt, the mixture was diluted with EtOAc and poured in a 2M aq NaOH solution. The phases were separated and the organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 95:5) afforded **1541** as a light yellow solid (35 mg, 28% over two steps). UPLC/MS(ES^+), m/z : 411.21 $[\text{M}+\text{H}]^+$.

EXAMPLE 16-1

Preparation of General Compound 1600A



[0922] Thionyl chloride (64.8 mL, 892 mmol) was added to a suspension of vanillic acid (15.0 g, 89.2 mmol) in MeOH (150 mL), which had been pre-cooled to 0°C .

The mixture was allowed to gradually reach rt and stirred for 18 h. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and washed with saturated aq NaHCO₃ solution and brine. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude methylester (18 g), which was used in the next step without further purification. The methylester was dissolved in DMF (80 mL). K₂CO₃ (36.9 g, 267 mmol) and 2-bromoethanol (13.4 g, 107 mmol) were added. The mixture was heated to 90°C for 2 h, cooled down to room temp and stirred for a further 18 h. A 1M aq HCl solution was added and the aqueous portion was extracted twice with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **16-2** as a white solid (12.0 g, 55% over two steps). UPLC/MS(ES⁺), m/z: 227.16 [M+H]⁺.

[0923] Sodium hydride (2.54 g, 63.6 mmol) was added to a solution of **16-2** (12.0 g, 53.0 mmol) in DMF (60 mL), which had been pre-cooled to 0°C. After 10 mins, 1-(chloromethyl)-4-methoxybenzene (10.8 mL, 79.5 mmol) was added and the mixture was stirred at rt for 1 h. The mixture was poured into a saturated aq NH₄Cl solution; and the aqueous portion was extracted twice with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude PMB-ether, which was used in the next step. The PMB-ether was dissolved in a 2:1:1 THF-MeOH-H₂O mixture (250 mL) and treated with LiOH·H₂O (6.68 g, 159 mmol). After 18 h of stirring at rt, the organic solvents were removed under reduced pressure. The supernatant aqueous portion was acidified with 1M aq HCl solution. A precipitate formed, and the white solid was collected, washed with Et₂O and dried to afford **16-3** (14.9 g, 84%). UPLC/MS(ES⁻), m/z: 331.22 [M+H]⁺.

[0924] A mixture of **16-3** (12.0 g, 36.1 mmol), EDC (9.69 g, 50.5 mmol), HOBT (8.78 g, 65.0 mmol), glycine methyl ester hydrochloride (6.80 g, 54.1 mmol) and TEA (14.1 mL, 101 mmol) in DCM (250 mL) was stirred at rt for 3 h. A 1M aq HCl solution was added; and the precipitate was filtered off. The phases were separated and the organic portion was washed with 1M aq HCl solution, dried (Na₂SO₄) and filtered. The volatiles were removed under reduced pressure to afford the crude amide (16.0 g), which was used in the next step. The amide was dissolved in a 2:1:1 THF-MeOH-H₂O solution (160 mL) and treated with LiOH·H₂O (6.06 g, 144 mmol). After 18 h of stirring at rt, the organic solvents

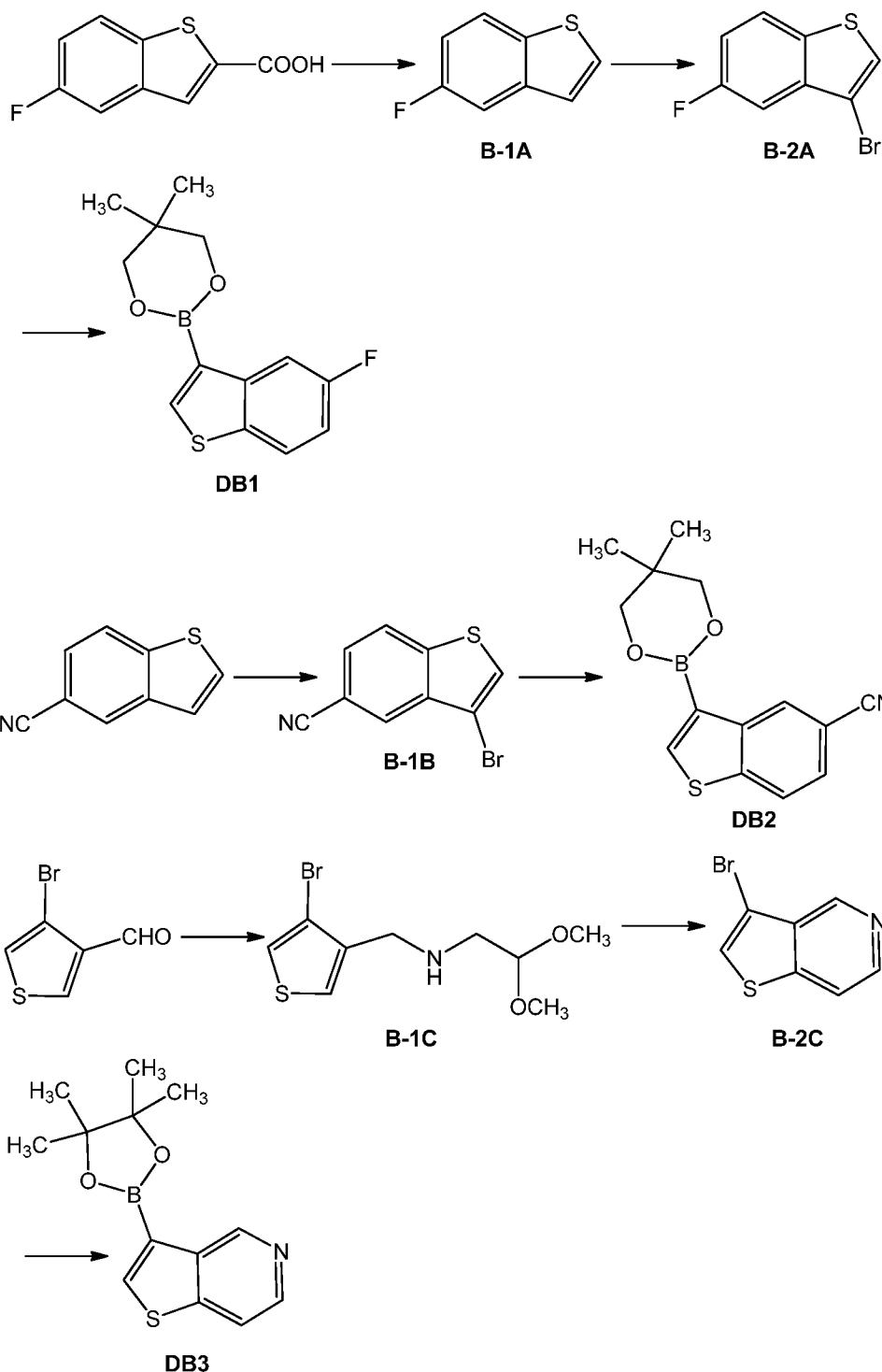
were removed under reduced pressure. The aqueous portion was acidified with 1M aq HCl solution; and formation of a white precipitate was observed. The white solid was collected, washed with water and Et₂O and dried to afford **16-4** (13.1 g, 93% over two steps). UPLC/MS(ES⁺), m/z: 390.15 [M+H]⁺.

[0925] A mixture of **16-4** (13.1 g, 33.8 mmol), EDC (9.06 g, 42.3 mmol), HOBT (8.21 g, 60.8 mmol), N,O-dimethylhydroxylamine hydrochloride (4.94 g, 50.6 mmol) and TEA (13.1 mL, 94.5 mmol) in DCM (250 mL) was stirred at rt for 2 h. A 1M aq HCl solution was added; and the layers were separated. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc) afforded the **16-5** as a white solid (25.3 g, 94%). UPLC/MS(ES⁺), m/z: 433.19 [M+H]⁺.

[0926] *i*-PrMgCl (2M solution in THF, 6.94 mL, 13.9 mmol) was added to a solution of **16-5** (3.00 g, 6.94 mmol) and **15-1** (3.26 g, 10.4 mmol) in THF (35 mL). The mixture was stirred at rt for 30 mins. The reaction was quenched with a saturated aq NH₄Cl solution and extracted with EtOAc. The organic portion was dried (Na₂SO₄), filtered and the volatiles were removed under reduced pressure. Chromatography of the residue (DCM-MeOH, 99:1) afforded **16-6** as a light yellow solid (2.26 g, 58%). UPLC/MS(ES⁺), m/z: 559.09 [M+H]⁺.

[0927] A mixture of **16-6** (0.390 mmol), boronic acid/ester (0.975 mmol), Pd(dppf)Cl₂ (0.019 mmol) and aq Na₂CO₃ (2M solution, 1.17 mmol) in DME (7 mL) was degassed and heated to 85°C for 2 h (or until disappearing of the starting material). The volatiles were removed under reduced pressure. Chromatography of the residue afforded the title compound. This compound was dissolved in a 10:1 DCM-TFA mixture and the solution was stirred at rt until disappearing of the starting material. A 2M aq NaOH solution was added (final pH 9) and the layers were separated. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue afforded Compound **1600A**.

EXAMPLE 16-2
Preparation of 1,3,2-Dioxaborinanes



[0928] A mixture of 5-fluoro-1-benzothiophene-2-carboxylic acid (500 mg, 2.54 mmol) and powdered copper (110 mg, 3.81 mmol) in quinoline (2.3 mL) was stirred with heat at 150°C for 20 h. After cooling to rt, the reaction was partitioned between EtOAc and

2N aq HCl solution. The phases were separated, and the organic portion was washed with 2N aq HCl, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue, **B-1A** (340 mg) was directly progressed to the next step.

[0929] A mixture **B-1A** (340 mg) and NBS (238 mg, 1.34 mmol) in a 25:1 DCM-DMF solution was stirred at rt for 16 h. The mixture was washed with 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ sol, 1M aq HCl and brine. The mixture was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue **B-2A** (284 mg) was directly progressed to the next step.

[0930] A mixture of **B-2A** (284 mg), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (505 mg, 2.24 mmol), KOAc (329 mg, 3.35 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (41 mg, 0.056 mmol) in DMF (2 mL) was stirred with heat at 90°C for 1.5 h. After cooling down to rt, the mixture was diluted with water and extracted with DCM. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) afforded **DB1** as a light yellow solid (150 mg, 22% over three steps). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.99 (s, 6 H), 3.82 (s, 4 H), 7.24 (td, $J=8.8$, 2.6 Hz, 1 H), 7.96 (dd, $J=10.5$, 2.5 Hz, 1 H), 8.05 (dd, $J=8.8$, 5.3 Hz, 1 H), 8.26 (s, 1 H).

[0931] A mixture 1-benzothiophene-5-carbonitrile (200 mg, 1.25 mmol), NBS (268 mg, 1.50 mmol) in a 25:1 DCM-DMF mixture (5.2 mL) was stirred at rt for 24 h. The mixture was washed with 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ solution, 1M aq HCl sol and brine. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude **B-1B** (300 mg) was progressed to the next step without further purification.

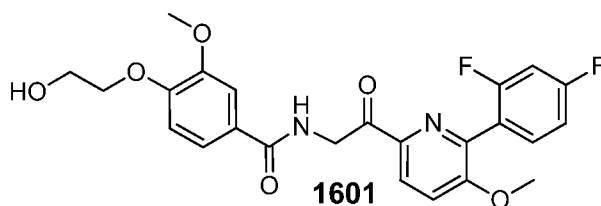
[0932] A mixture of **B-1B** (120 mg), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (170 mg, 0.752 mmol), KOAc (147 mg, 1.20 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (36.5 mg, 0.050 mmol) in DMF (2 mL) was deoxygenated and heated to 90 °C. After 3.5 h the mixture was diluted with water; and the aqueous portion was extracted with DCM. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue(cyclohexane-EtOAc, 100:0 to 80:20) afforded **DB2**.

[0933] 4-bromothiophene-3-carbaldehyde (500 mg, 2.60 mmol) was dissolved in EtOH (6 mL) and treated with 2,2-dimethoxyethan-1-amine (275 mg, 2.60 mmol) and 4-methylbenzene-1-sulfonic acid monohydrate (24.7 mg, 0.130 mmol). The mixture was

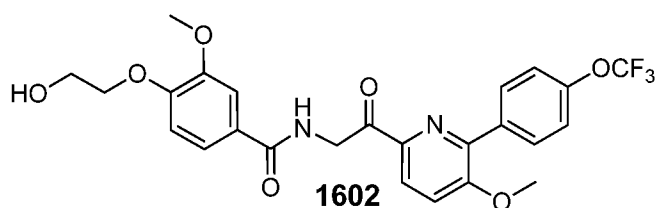
heated to reflux. After 4 h, the mixture was cooled to rt and NaBH₄ (95.0 mg, 2.60 mmol) was added portionwise. The mixture was stirred rt for 15 min, and then heated to reflux. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc, washed with saturated aq. NaHCO₃, water and brine. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude **B-1C** was progressed to the next step without any further purification. UPLC/MS(ES⁺), m/z: found 280.05 [MH⁺], C₉H₁₄BrNO₂S requires 278.99. t_R: 0.36 min.

[0934] 4-Methylbenzene-1-sulfonyl chloride (594 mg, 3.12 mmol) was added to a solution of **B-1C** and pyridine (617 mg, 7.80 mmol) in DCM (5 mL) which had been pre-cooled to 0 °C. The mixture was stirred at 0°C for 4 h. The mixture was then washed 3 times with 1M aq HCl solution, water and saturated aq. NaHCO₃ solution. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) afforded the sulphonamide (660 mg, 58% over two steps). The sulphonamide was dissolved in 1,4-dioxane (4 mL) and treated with 6N aq HCl solution. The mixture was heated to 100°C and stirred for 18 h. The volatiles were removed under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 90:10) afforded **B-2C** as a colourless oil (120 mg).

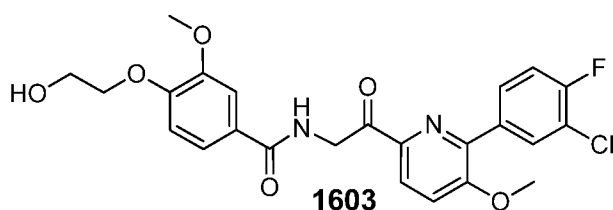
[0935] A mixture of **B-2C** (120 mg), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (426 mg, 1.68 mmol), KOAc (164 mg, 1.68 mmol) and Pd(dppf)Cl₂ (20.0 mg, 0.028 mmol) in DMF (2 mL) was degassed and heated to 90 °C. After 2 h, volatiles were removed under reduced pressure. The crude **DB3** was used without further purification.



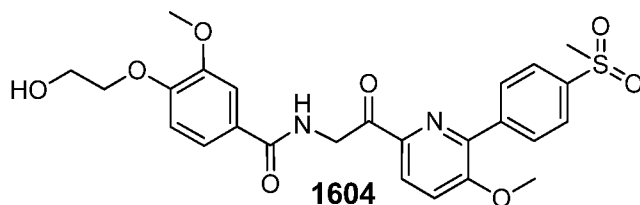
[0936] Compound **1601** was obtained by reacting **16-6** with 2,4-difluorophenylboronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1601** was obtained as a yellow solid (47% over two steps). UPLC/MS(ES⁺), m/z: 473.16 [M+H]⁺.



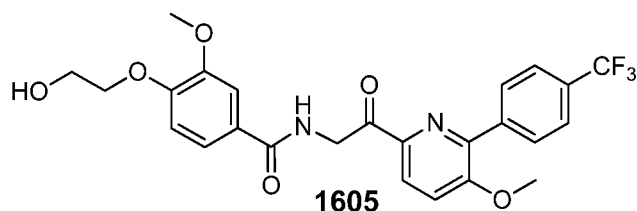
[0937] Compound **1602** was obtained by reacting **16-6** with [4-(trifluoromethoxy)phenyl]boronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1602** was obtained as a white solid (57% over two steps). UPLC/MS(ES^+), m/z : 521.12 $[\text{M}+\text{H}]^+$.



[0938] Compound **1603** was obtained by reacting **16-6** with (3-chloro-4-fluorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1603** was obtained as a white solid (24% over two steps). UPLC/MS(ES^+), m/z : 489.13 $[\text{M}+\text{H}]^+$.

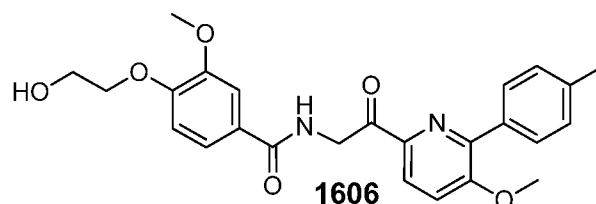


[0939] Compound **1604** was obtained by reacting **16-6** with (4-methanesulfonylphenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1604** was obtained as a white solid (52% over two steps). UPLC/MS(ES^+), m/z : 515.15 $[\text{M}+\text{H}]^+$.

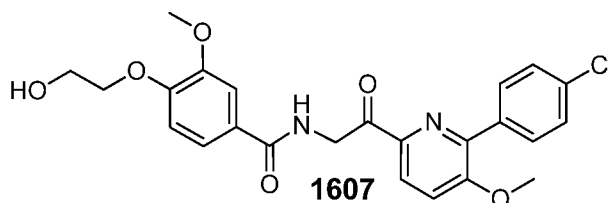


[0940] Compound **1605** was obtained by reacting **16-6** with [4-(trifluoromethyl)phenyl]boronic acid followed by PMB-group according to the procedure

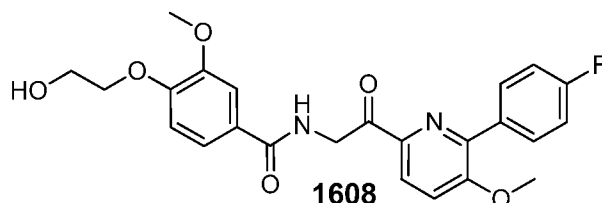
shown in Example 16-1. Compound **1605** was obtained as a white solid (20% over two steps). UPLC/MS(ES⁺), m/z: 505.13 [M+H]⁺.



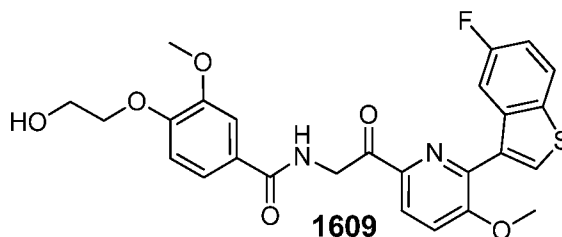
[0941] Compound **1606** was obtained by reacting **16-6** with 4-(methylphenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1606** was obtained as a light yellow solid (58% over two steps). UPLC/MS(ES⁺), m/z: 451.21 [M+H]⁺.



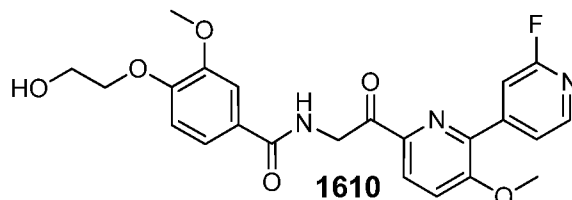
[0942] Compound **1607** was obtained by reacting **16-6** with (4-chlorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1607** was obtained as a light yellow solid (50% over two steps). UPLC/MS(ES⁺), m/z: 471.13 [M+H]⁺.



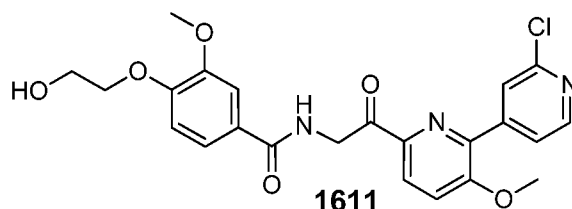
[0943] Compound **1608** was obtained by reacting **16-6** with (4-fluorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1608** was obtained as a light yellow solid (40% over two steps). UPLC/MS(ES⁺), m/z: 455.15 [M+H]⁺.



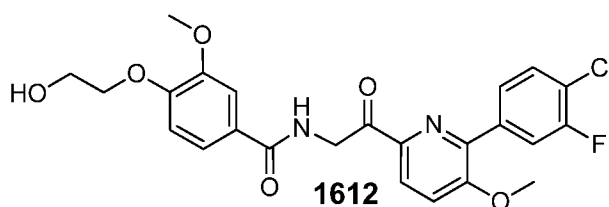
[0944] Compound **1609** was obtained by reacting **16-6** with 2-(5-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane followed by PMB-group according to the procedure shown in Example 16-1. Compound **1609** was obtained as a light yellow solid (69% over two steps). UPLC/MS(ES^+), m/z : 511.22 $[\text{M}+\text{H}]^+$.



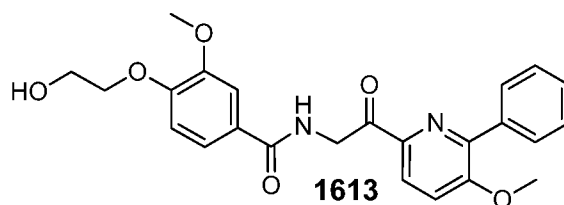
[0945] Compound **1610** (29% over two steps) was obtained by reacting **16-6** with (2-fluoropyridin-4-yl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 456.11 $[\text{M}+\text{H}]^+$.



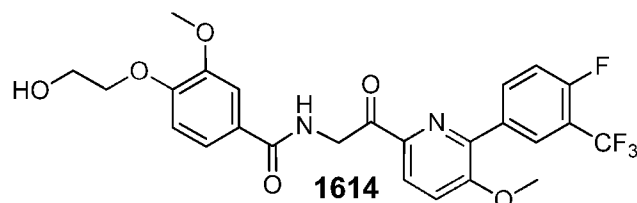
[0946] Compound **1611** (28% over two steps) was obtained by reacting **16-6** with (2-chloropyridin-4-yl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 472.14 $[\text{M}+\text{H}]^+$.



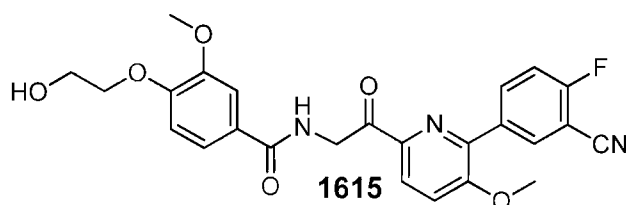
[0947] Compound **1612** was obtained by reacting **16-6** with (4-chloro-3-fluorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. Compound **1612** was obtained as an off-white solid (33% over two steps). UPLC/MS(ES^+), m/z : 489.08 $[\text{M}+\text{H}]^+$.



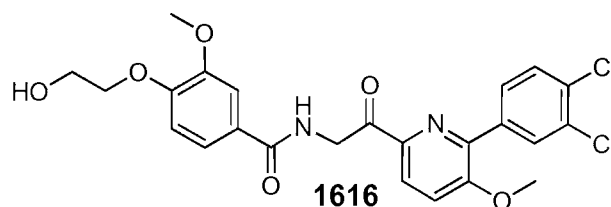
[0948] Compound **1613** (71% over two steps) was obtained by reacting **16-6** with phenylboronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES⁻), m/z: 437.19 [M+H]⁻.



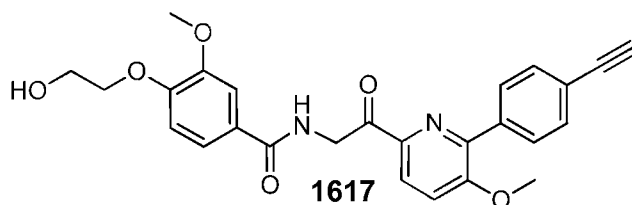
[0949] Compound **1614** (64% over two steps) was obtained by reacting **16-6** with [4-fluoro-3-(trifluoromethyl)phenyl]boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES⁻), m/z: 523.15 [M+H]⁻.



[0950] Compound **1615** (56% over two steps) was obtained by reacting **16-6** with (3-cyano-4-fluorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES⁺), m/z: 480.18 [M+H]⁺.

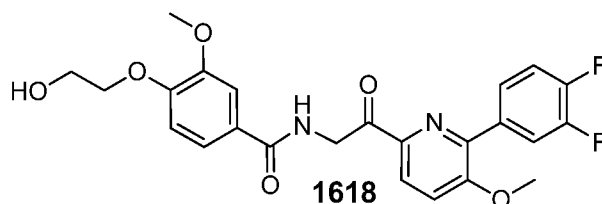


[0951] Compound **1616** (52% over two steps) was obtained by reacting **16-6** with (3,4-dichlorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES⁻), m/z: 505.05 [M+H]⁻.

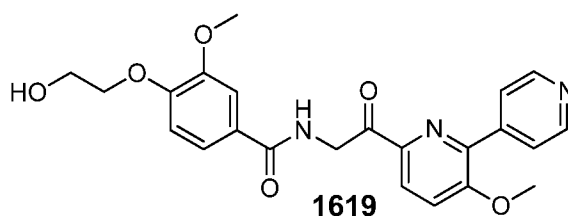


[0952] Compound **1617** (15% over two steps) was obtained by reacting **16-6** with trimethyl({2-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethynyl})silane followed by

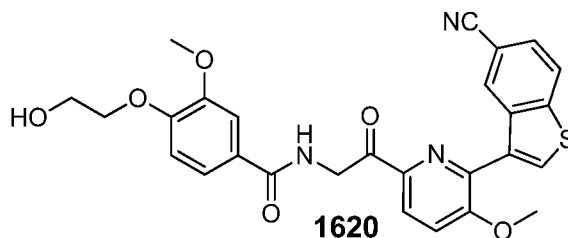
PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 461.19 $[\text{M}+\text{H}]^+$.



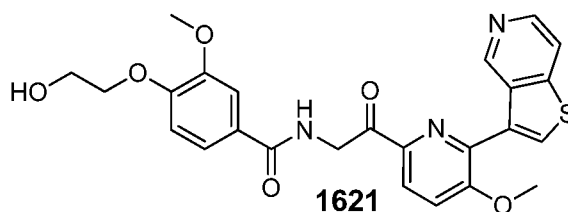
[0953] Compound **1618** (61% over two steps) was obtained by reacting **16-6** (3,4-difluorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 473.19 $[\text{M}+\text{H}]^+$.



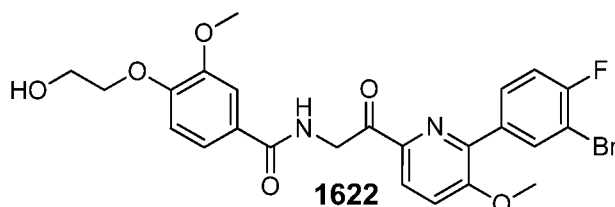
[0954] Compound **1619** (55% over two steps) was obtained by reacting **16-6** with (3,4-difluorophenyl)boronic acid (pyridin-4-yl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 438.25 $[\text{M}+\text{H}]^+$.



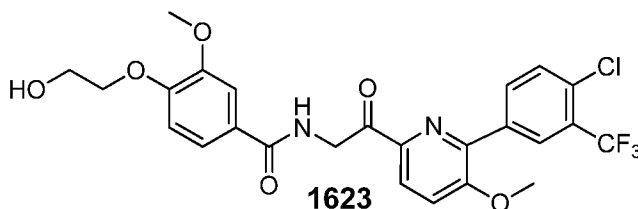
[0955] Compound **1620** (27% over two steps) was obtained by reacting **16-6** with 3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-benzothiophene-5-carbonitrile followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 518.15 $[\text{M}+\text{H}]^+$.



[0956] Compound **1621** (37% over two steps) was obtained by reacting **16-6** with 3-(tetramethyl-1,3,2-dioxaborolan-2-yl)thieno[3,2-c]pyridine followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 494.19 $[\text{M}+\text{H}]^+$.



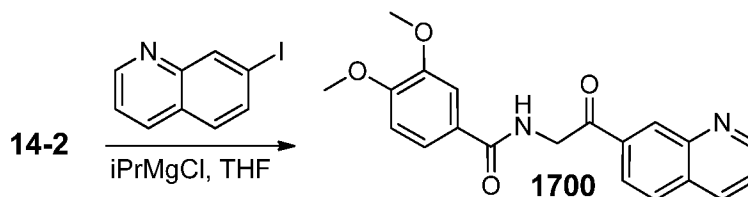
[0957] Compound **1622** (18% over two steps) was obtained by reacting **16-6** with (3-bromo-4-fluorophenyl)boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 533.16 $[\text{M}+\text{H}]^+$.



[0958] Compound **1623** (78% over two steps) was obtained by reacting **16-6** with [4-chloro-3-(trifluoromethyl)phenyl]boronic acid followed by PMB-group according to the procedure shown in Example 16-1. UPLC/MS(ES^+), m/z : 539.18 $[\text{M}+\text{H}]^+$.

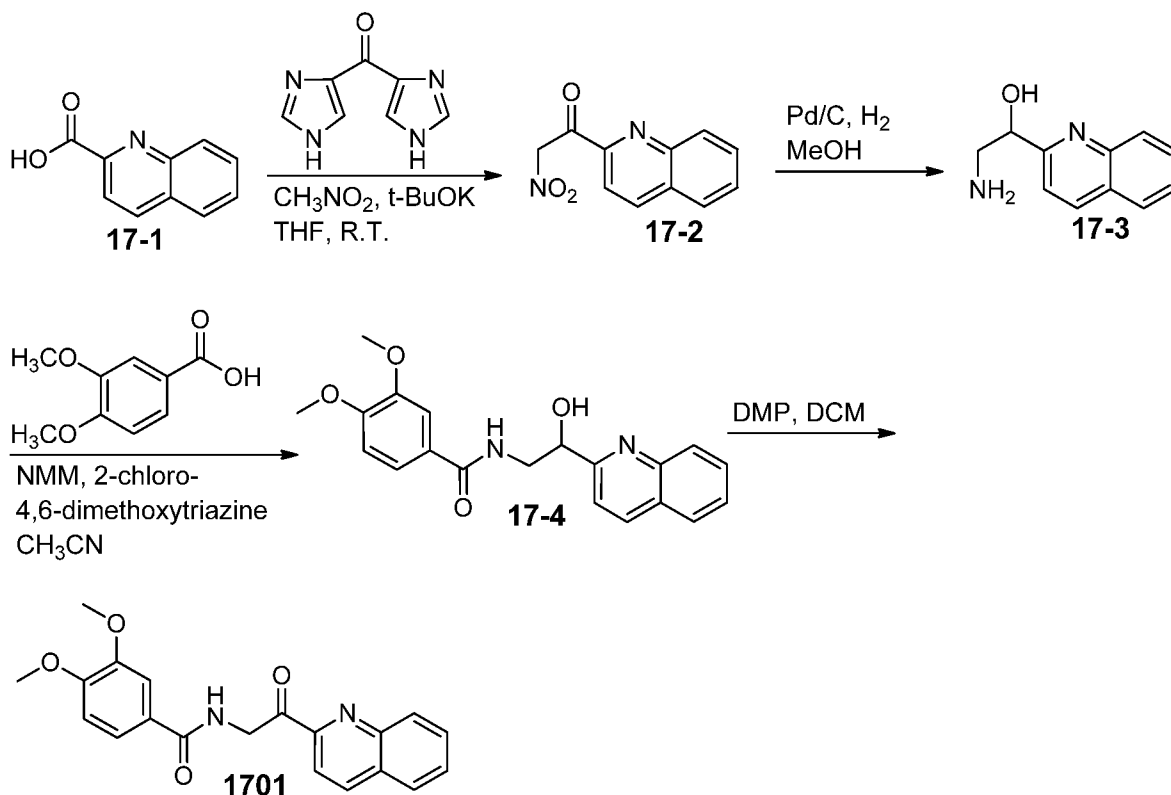
EXAMPLE 17-1

Preparation of Compound 1700



[0959] A 2M *i*-PrMgCl solution in THF (1.22 mL, 2.45 mmol) was added dropwise to a mixture of 7-iodoquinoline (267 mg, 1.05 mmol) and **14-2** (200 mg, 0.700 mmol) in THF (9 mL). The mixture was stirred at rt for 15 mins. Water was added and the organic solvents were removed under reduced pressure. The aqueous portion was extracted with EtOAc. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 30:70) afforded compound **1700** (44 mg, 18%). UPLC/MS(ES^+), m/z : 351.13 $[\text{M}+\text{H}]^+$.

EXAMPLE 17-2
Preparation of Compound 1701



[0960] 1,1'-Carbonyldiimidazole (1.17 g, 7.21 mmol) was added to a solution of **17-1** (1.00 g, 5.77 mmol) in THF (9.6 mL). The mixture was stirred at rt for 30 mins. CH_3NO_2 (1.87 mL, 34.62 mmol) and potassium *tert*-butoxide (2.58 g, 23.04 mmol) were then added, and the mixture was stirred for 2 h. The volatiles were removed under reduced pressure. EtOAc (50 mL) and 0.1M aq HCl solution (40 mL) were added. The yellow precipitate was collected and dried to afford **17-2** (1.13 g, 91%). UPLC/MS(ES^+), m/z : 217.05 $[\text{M}+\text{H}]^+$.

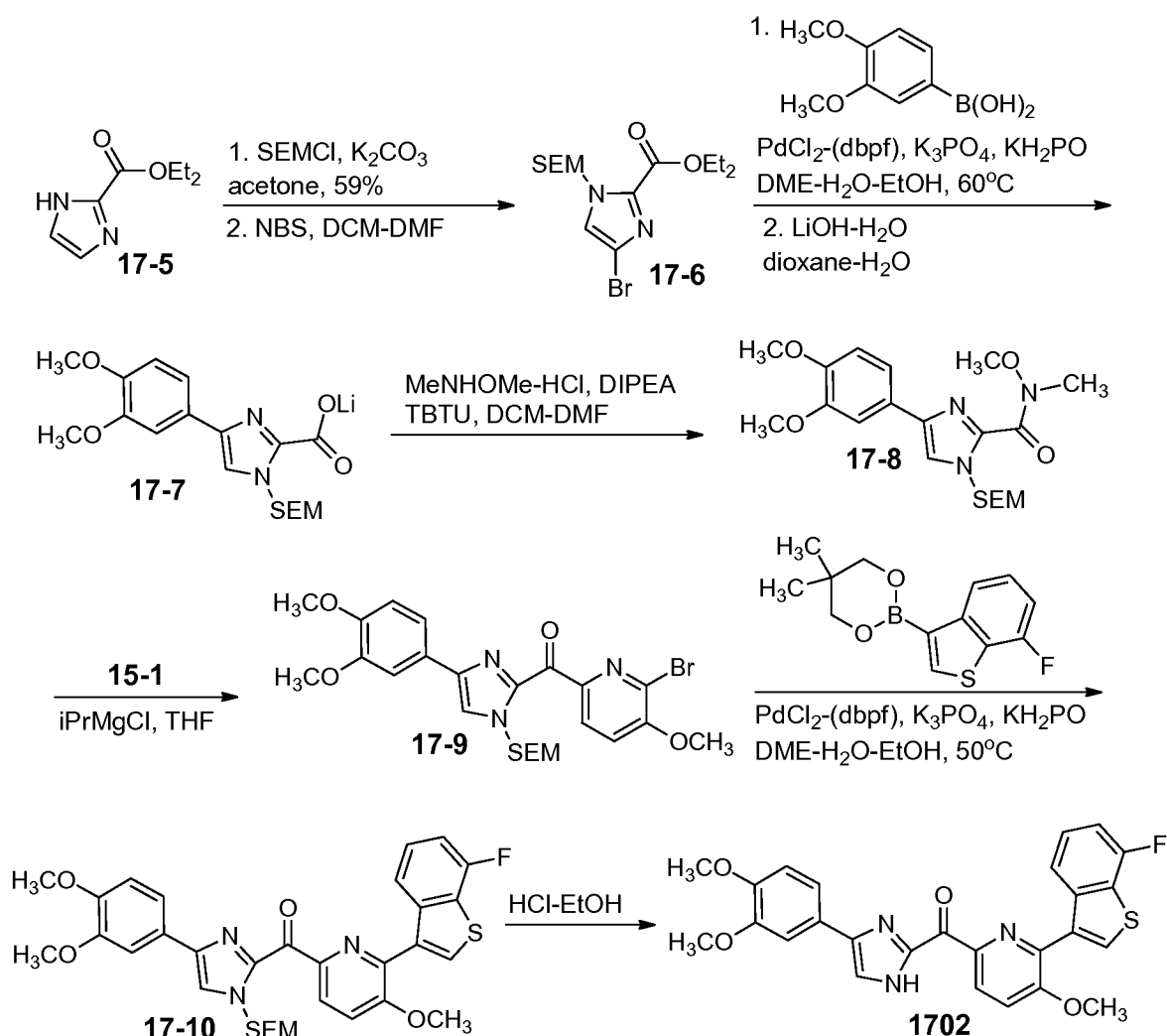
[0961] A mixture of 10% Pd/C (Degussa type, 60 mg) and **17-2** (60 mg, 0.270 mmol) in MeOH (9 mL) was stirred under H_2 atmosphere for 1.5 h. The catalyst was filtered off and the organic portion was concentrated under reduced pressure to afford crude **17-3** (50 mg), which was directly in the next step.

[0962] A mixture of 3,4-dimethoxybenzoic acid (76 mg, 0.420 mmol), 4-methylmorpholine (57 μL , 0.52 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (63 mg, 0.36 mmol) in CH_3CN (4 mL) was stirred at rt for 1 h. **17-3** (50 mg) was added, and the

mixture was stirred for 18 h. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc, and the organic portion was washed twice with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 70:30 to 0:100) afforded **17-4** as a grey solid (74 mg, 78% over two steps). UPLC/MS(ES^+), m/z : 353.15 $[\text{M}+\text{H}]^+$.

[0963] DMP (135 mg, 0.320 mmol) was added to a solution of **17-4** (74 mg, 0.21 mmol) in DCM (4 mL). After 1 h, the reaction was quenched with a 1:1 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ solution, saturated aq NaHCO_3 . The mixture was stirred for 30 mins. The aqueous portion was extracted with EtOAc. The combined organic portions were dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane:EtOAc, 100:0 to 60:40) afforded compound **1701** as a yellowish solid (21 mg, 28%). UPLC/MS(ES^+), m/z : 351.15 $[\text{M}+\text{H}]^+$.

EXAMPLE 17-3
Preparation of Compound 1702



[0964] [2-(chloromethoxy)ethyl]trimethylsilane (3.23 mL, 18.2 mmol) was added to a stirred suspension of **17-5** (2.13 g, 15.2 mmol) and potassium carbonate (4.20 g, 30.4 mmol) in acetone (30 mL), and the mixture was stirred overnight at rt. The mixture was poured into water (100 mL) and EtOAc/cyclohexane (200 mL, 1:1). The phases were separated and the aqueous phase extracted with EtOAc/cyclohexane (100 mL, 1:1). The combined organic phases were washed with brine (50 mL), dried (Na₂SO₄) and evaporated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 90:10 to 40:60) afforded a SEM-protected intermediate as a colourless oil (2.43 g, 59%). This compound was dissolved in a 1:1 DCM-DMF (20 mL) and N-bromosuccinimide (2.40 g, 13.5 mmol) was added. The mixture was stirred overnight. The mixture was poured into

water (100 mL) and 10% sodium thiosulphate solution (5 mL), and then extracted with EtOAc/cyclohexane (100 mL + 50 mL, 1:1). The combined organic phases were washed with water/brine (2 x 100 mL, 1:1) and brine (100 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 95:5 to 80:20) afforded **17-6** as a white solid (1.86 g, 60%). UPLC/MS(ES^+), m/z : 349.07 $[\text{M}+\text{H}]^+$.

[0965] A solution of monobasic potassium phosphate (0.69 g, 5.07 mmol) and tribasic potassium phosphate (1.08 g, 5.07 mmol) in water (20 mL) was added to a solution of (3,4-dimethoxyphenyl)boronic acid (1.20 g, 6.59 mmol) and **17-6** (1.77 g, 5.07 mmol) in DME (35 mL) and EtOH (10 mL) at rt. The mixture was deoxygenated, $\text{Pd}(\text{dbpf})\text{Cl}_2$ (120 mg, 0.250 mmol) was added, and the mixture was stirred at 60°C for 3 h. Additional $\text{Pd}(\text{dbpf})\text{Cl}_2$ (240 mg, 0.500 mmol) was added and the mixture was stirred at 60°C for 6 h. The mixture was partially evaporated under reduced pressure to remove the majority of the EtOH and DME. The residue was partitioned between EtOAc (150 mL) and half-saturated sodium bicarbonate solution (100 mL). The aqueous phase was extracted further with EtOAc (50 mL), and the combined organic phases were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Chromatography of the residue (SNAP 100 using NH samplet, cyclohexane-EtOAc, 80:20 to 50:50) afforded the coupled intermediate as a pale yellow gum (1.61 g, 78%). This was dissolved in 1,4-dioxane (30 mL) and a solution of lithium hydroxide monohydrate (0.18 g, 4.36 mmol) in water (10 mL) was added. The mixture was heated to 50°C for 4 h. The mixture was evaporated under reduced pressure to give **17-7** as a white solid (1.60 g, ~95 wt%).

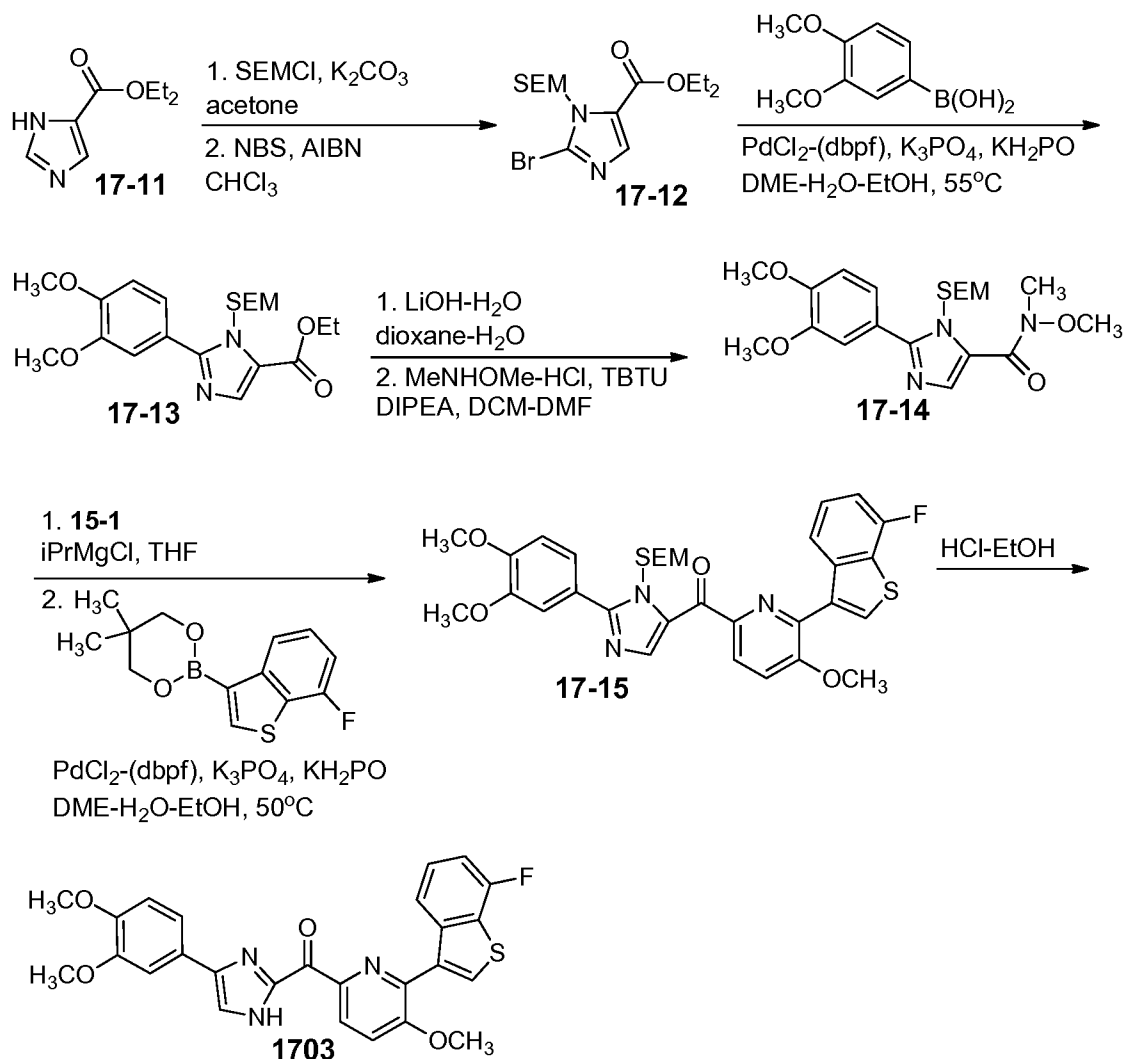
[0966] TBTU (1.65 g, 5.14 mmol) was added to a stirred suspension of **17-7** (1.60 g), methoxy(methyl)amine hydrochloride (0.460 g, 4.74 mmol) and DIPEA (1.38 mL, 7.90 mmol) in a 1:1 DCM-DMF mixture (50 mL). After 30 mins, additional TBTU (2 x 200 mg) was added at 20 minute intervals after which the mixture became a homogeneous solution. The mixture was diluted with EtOAc (250 mL), washed with half saturated sodium bicarbonate solution (2 x 200 mL) and brine (200 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 90:10 to 50:50) afforded **17-8** as a pale yellow gum (1.57 g, 94%). UPLC/MS(ES^+), m/z : 422.20 $[\text{M}+\text{H}]^+$.

[0967] A 2M *i*-PrMgCl solution in THF (0.46 mL, 0.920 mmol) was added dropwise to a stirred solution of **15-1** (268 mg, 0.850 mmol) in THF (3 mL) at -5°C. The solution was stirred at -5°C for 30 mins, then a solution of **17-8** (300 mg, 0.710 mmol) in THF (3 mL) was added. Stirring was continued for 90 mins allowing the temperature to reach 0°C. The reaction was quenched with water (5 mL), partitioned between EtOAc (50 mL) and half-saturated brine (50 mL). The aqueous phase was extracted further with EtOAc (25 mL). The combined organic phases were washed with brine (25 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was chromatographed on NH-modified silica gel eluting with a gradient of 10-50% EtOAc in cyclohexane to give **17-9** as an intense yellow gum/foam (305 mg, 78%). UPLC/MS(ES⁺), m/z: 548.13 [M+H]⁺.

[0968] A solution of monobasic potassium phosphate (75 mg, 0.550 mmol) and tribasic potassium phosphate (117 mg, 0.550 mmol) in water (4 mL) was added to a solution of 2-(7-fluoro-1-benzothiophen-4-yl)-5,5-dimethyl-1,3,2-dioxaborinane (261 mg, 0.990 mmol) and **17-9** (302 mg, 0.550 mmol) in DME (6 mL) and EtOH (2 mL) at rt. The mixture was deoxygenated with N₂ before the addition of Pd(dbpf)Cl₂ (13 mg, 0.027 mmol). The mixture was then stirred at 60°C for 2 h. The mixture was partially evaporated under reduced pressure to remove most of the DME and EtOH. The residue was partitioned between EtOAc (50 mL) and half-saturated sodium bicarbonate solution (30 mL). The aqueous phase was extracted further with EtOAc (25 mL), and the combined organic phases were washed with brine (30 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was chromatographed on NH-modified silica gel eluting with a gradient of 10-60% EtOAc in cyclohexane to give the **17-10** as an intense yellow gum/foam (301 mg, 88%). UPLC/MS(ES⁺), m/z: 620.20 [M+H]⁺.

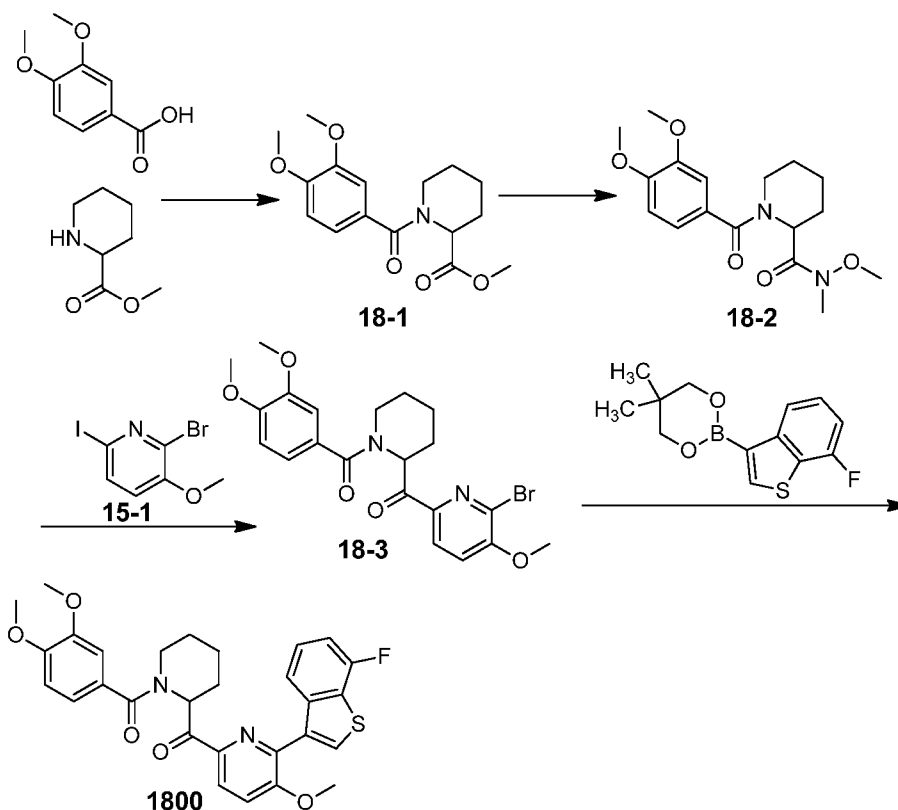
[0969] A 1M aq HCl solution (15 mL) was added to a stirred solution of **17-10** (298 mg, 0.480 mmol) in EtOH (15 mL). The mixture was then heated to 50°C for 8 h. The mixture was partially evaporated under reduced pressure to remove most of the EtOH. The residue was basified with 1M aq NaOH solution and extracted with dichloromethane (50 + 25 mL). The combined organic phases were washed with brine (25 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was chromatographed on NH-modified silica gel eluting with a gradient of 50-100% EtOAc in cyclohexane to give compound **1702** as an intense yellow gum/foam (219 mg, 93%). UPLC/MS(ES⁺), m/z: 490.20 [M+H]⁺.

EXAMPLE 17-4
Preparation of Compound 1703



[0970] Compound **1703** was prepared starting from ethyl 1H-imidazole-5-carboxylate by following a synthetic route, which closely follows that described for preparation of compound **1702**. Compound **1703** was obtained as a pale yellow solid. UPLC/MS(ES^+), m/z : 490.20 $[M+H]^+$.

EXAMPLE 18-1
Preparation of Compound 1800



[0971] A mixture of 3,4-dimethoxybenzoic acid (550 mg, 3.02 mmol), NMM (530 μ L, 4.83 mmol) and 2-chloro-4,6-dimethoxytriazine (740 mg, 4.23 mmol) in CH_3CN (20 mL) was stirred at rt for 30 mins. Methyl piperidine-2-carboxylate (605 mg, 4.23 mmol) was added and the mixture was left to stir at rt for 1 h. DCM was added and the organic portion was washed with 1M aq HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 50:50 to 0:100) afforded **18-1** as a colourless wax (529 mg, 57%). UPLC/MS(ES^+), m/z : 308.15 $[\text{M}+\text{H}]^+$.

[0972] Compound **18-1** (529 mg, 1.72 mmol) was suspended in a 2:1:1 THF-MeOH- H_2O mixture (6 mL) and treated with LiOH- H_2O (217 mg, 5.18 mmol). After 1 h stirring at rt, the mixture was concentrated under reduced pressure. The residue was taken up with EtOAc and water. The layers were separated and the aqueous portion was acidified with 1M aq HCl solution and extracted twice with EtOAc. The combined organic portions

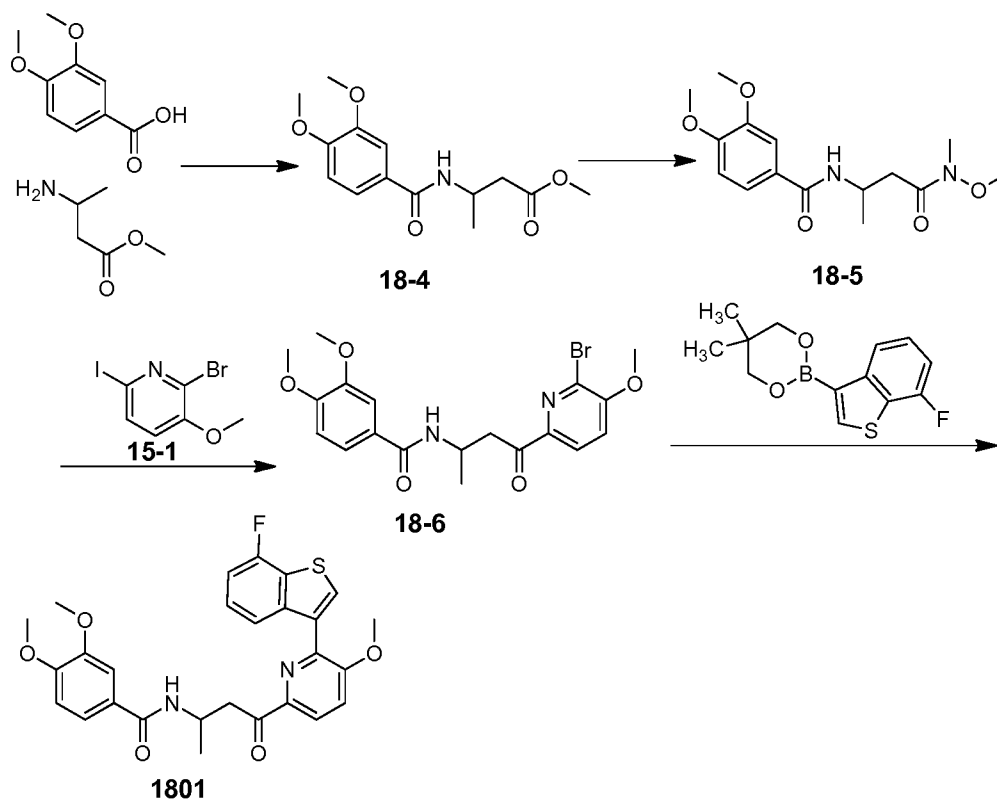
were dried (Na₂SO₄), filtered and the volatiles were removed under reduced pressure. The crude acid was directly used in to the next step.

[0973] The crude acid was dissolved in CH₃CN (15 mL). To the solution, NMM (251 uL, 2.28 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (350 mg, 2.00 mmol) were added. After 30 mins, a mixture of *N,O*-dimethylhydroxylamine hydrochloride (217 mg, 2.24 mmol) and NMM (204 uL, 1.86 mmol) in CH₃CN (2 mL) was added, and the mixture was stirred at rt for 2 h. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and the organic portion was washed with 1M aq HCl solution and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-2** was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.35 - 1.94 (m, 5 H), 2.09 (d, *J*=12.5 Hz, 1 H), 3.24 (br. s., 3 H), 3.69 -4.01 (m, 11 H), 5.56 (br. s., 1 H), 6.85 (d, *J*=8.5 Hz, 1 H), 6.96 -7.12 (m, 2 H).

[0974] A 2M *i*-PrMgCl solution in THF (173 uL, 3.57 mmol) was added dropwise to a mixture of **18-2** and **15-1** (670 mg, 2.14 mmol) in dry THF (7 mL). The mixture was stirred at rt for 1 h and then quenched with 1M aq HCl solution. EtOAc was added and the organic portion was washed with 1M aq HCl solution and water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **18-3** as a white foam (377 mg, 47% over three steps).

[0975] A mixture of **18-3** (220 mg, 0.476 mmol), 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (251 mg, 0.952 mmol), Pd(dppf)Cl₂ (29 mg, 0.024 mmol) and 2M aq Na₂CO₃ (714 uL, 1.43 mmol) in DCE (7 mL) was degassed and heated to 85°C for 2 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 80:20 to 30:70) afforded compound **1800** as a white solid (70.0 mg, 28%). UPLC/MS(ES⁺), *m/z*: 535.15 [M+H]⁺.

EXAMPLE 18-2
Preparation of Compound 1801



[0976] A mixture of 3,4-dimethoxybenzoic acid (359 mg, 1.97 mmol), 2-chloro-4,6-dimethoxytriazine (483 mg, 2.76 mmol) and NMM (346 μ L, 3.15 mmol) in CH_3CN (8 mL) was stirred at rt for 30 mins. Methyl 3-aminobutanoate (300 mg, 2.56 mmol) was added and the mixture was stirred at rt for an additional 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in DCM and the organic portion washed 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) **18-4** as a white solid (300 mg, 54%).

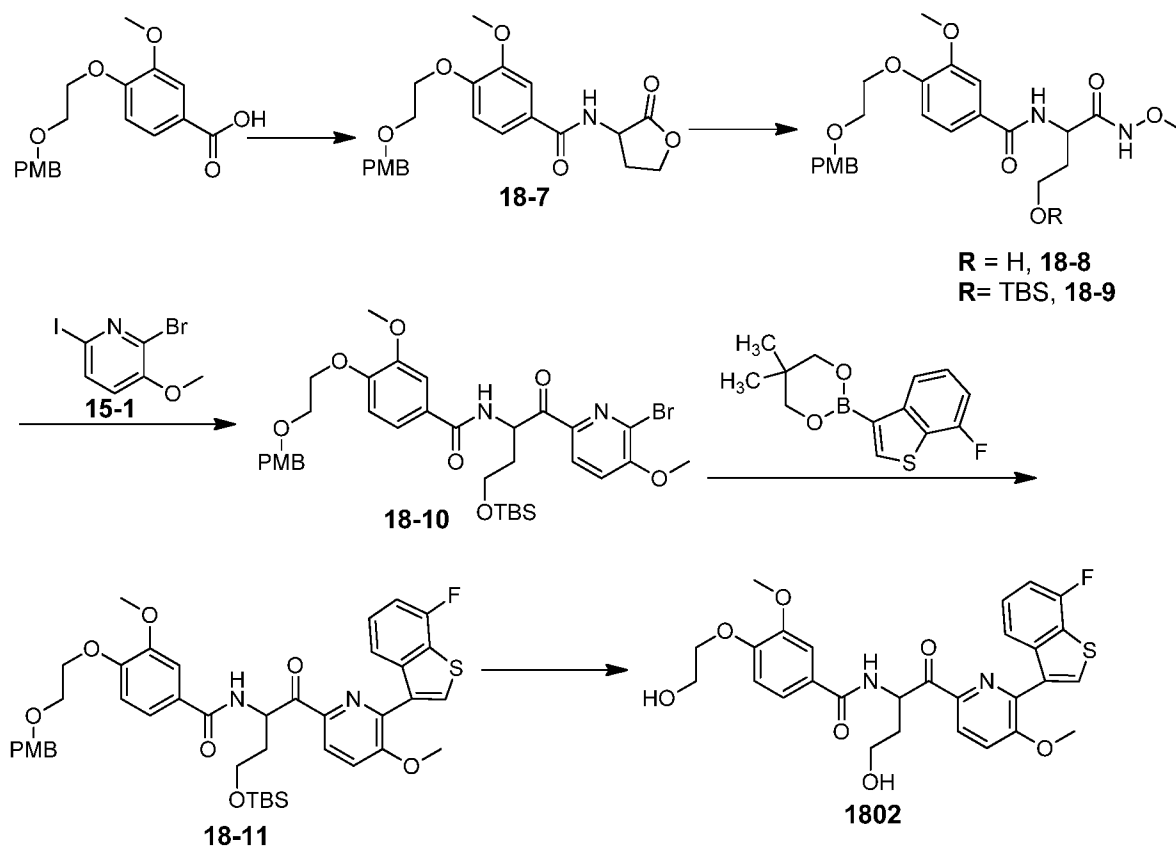
[0977] Compound **18-4** (300 mg, 1.06 mmol) was dissolved in a 2:1:1 THF-MeOH- H_2O mixture (10 mL) and treated with LiOH- H_2O (141 mg, 3.37 mmol). After 30 mins, the volatiles were removed under reduced pressure. The residue was partitioned between DCM and 1M aq HCl solution. The layers were separated and the organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the acid, which was used in the next step.

[0978] The acid was dissolved in CH₃CN (10 mL) and 2-chloro, 4,6-dimethoxytriazine (203 mg, 1.16 mmol) and NMM (237 μ L, 2.16 mmol) were sequentially added to the solution. After 30 mins, *N,O*-dimethyl hydroxylamine hydrochloride (105 mg, 1.08 mmol) was added and the mixture was stirred at room temp for an additional 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in DCM and the organic portion washed with 1M aq HCl solution, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 80:20) afforded **18-5** as a colourless wax (223 mg, 68% over two steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.15 -1.20 (m, 3 H), 2.54-2.65 (m, 1 H), 2.66 -2.77 (m, 1 H), 3.09 (s, 3 H), 3.31 (s, 3 H), 3.68 (s, 3 H), 3.80 (s, 3H), 4.31 -4.45 (m, 1 H), 7.00 (d, *J*=8.3 Hz, 1 H), 7.41 (d, *J*=1.8 Hz, 1 H), 7.45 (dd, *J*=8.3, 2.0 Hz, 1 H), 8.12 (d, *J*=8.0 Hz, 1 H).

[0979] A 2M *i*-PrMgCl solution in THF (900 μ L, 1.80 mmol) was added dropwise to a solution of **18-5** (223 mg, 0.719 mmol) and **15-1** (313 mg, 1.08 mmol) in THF (6 mL). The mixture was stirred at rt for 1 h and then quenched with 1M aq HCl solution. The aqueous portion was extracted twice with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 95:5) afforded **18-6** as a white solid (170 mg, 54%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.41 (d, *J*=6.8 Hz, 3 H), 3.28 (dd, *J*=16.3, 5.3 Hz, 1 H), 3.65 (dd, *J*=16.3, 6.1 Hz, 1 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 4.01 (s, 3 H), 4.70 (br. s., 1 H), 6.84 - 6.93 (m, 2 H), 7.23 (d, *J*=8.5 Hz, 1 H), 7.27-7.31 (m, 1 H), 7.43 (d, *J*=1.8 Hz, 1 H), 8.05 (d, *J*=8.5 Hz, 1 H).

[0980] A mixture of **18-6** (170 mg, 0.390 mmol), 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (257 mg, 0.975 mmol), Pd(dppf)Cl₂ (14 mg, 0.019 mmol) and 2M aq Na₂CO₃ (585 μ L, 1.17 mmol) in DCE (7 mL) was degassed and heated to 85°C for 2 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 50:50 to 0:100) afforded compound **1801** as an off-white solid (137 mg, 69%). UPLC/MS(ES⁺), *m/z*: 509.15 [M+H]⁺.

EXAMPLE 18-3
Preparation of Compound 1802



[0981] A mixture of 3-methoxy-4-{2-[(4-methoxyphenyl)methoxy]ethoxy}benzoic acid (500 mg, 1.50 mmol), 2-chloro-4,6-dimethoxytriazine (368 mg, 2.10 mmol) and NMM (334 μL , 2.40 mmol) in CH_3CN (10 mL) was stirred at rt for 30 mins. 2-Amino-4-hydroxybutanoic acid (232 mg, 1.95 mmol) was added, and the mixture was stirred at rt for 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in DCM and the organic portion was washed twice with 1M aq HCl solution. The combined organic portions were dried (Na_2SO_4), filtered and volatiles were removed under reduced pressure to afford **18-7** which was progressed to the next step without any further purification. UPLC/MS(ES^+), m/z : 416.20 $[\text{M}+\text{H}]^+$.

[0982] Pyridine (137 μL , 1.70 mmol) and AlMe_3 (2M solution in heptanes, 1.15 mL, 2.31 mmol) were added to a suspension of $\text{MeONHMe}\cdot\text{HCl}$ (224 mg, 2.31 mmol) in DCM (5 mL). The mixture was stirred under N_2 atmosphere for 15 mins. A solution of **18-7** in DCM (2 mL) was added dropwise. The mixture was stirred at rt for 2.5 h, cooled to 0°C and quenched with 1M aq HCl solution. The organic portion was diluted with DCM and

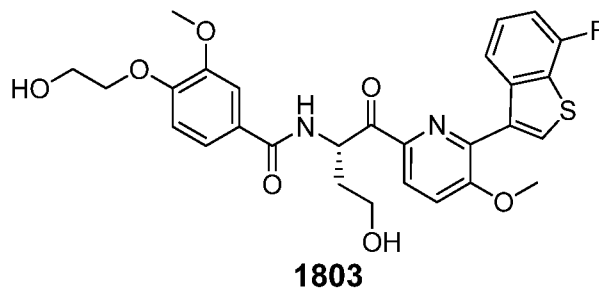
washed with 1M aq HCl sol and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-8** was used in the next step without further purification.

[0983] Triethylamine (214 uL, 1.54 mmol) and TBSCl (151 mg, 1.0 mmol) were sequentially added to a solution of **18-8** in DCM (6 mL). The mixture was stirred at rt for 48 h, diluted with DCM and washed with water. The organic portion was dried (Na₂SO₄), filtered and volatiles were removed under reduced pressure. Crude **18-9** (263 mg) was used in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.07, 0.08 (2 x s, 6 H), 0.91 (s, 9 H), 1.91 -2.01 (m, 1 H), 2.08 -2.20 (m, 1 H), 3.26 (s, 3 H), 3.76 -3.97 (m, 13 H), 4.25 (t, *J*=5.1 Hz, 2 H), 4.59 (s, 2 H), 5.15 -5.30 (m, 1 H), 6.84 -6.95 (m, 3 H), 7.11 -7.22 (m, 1 H), 7.30 -7.35 (m, 3 H), 7.45 (d, *J*=1.8 Hz, 1 H).

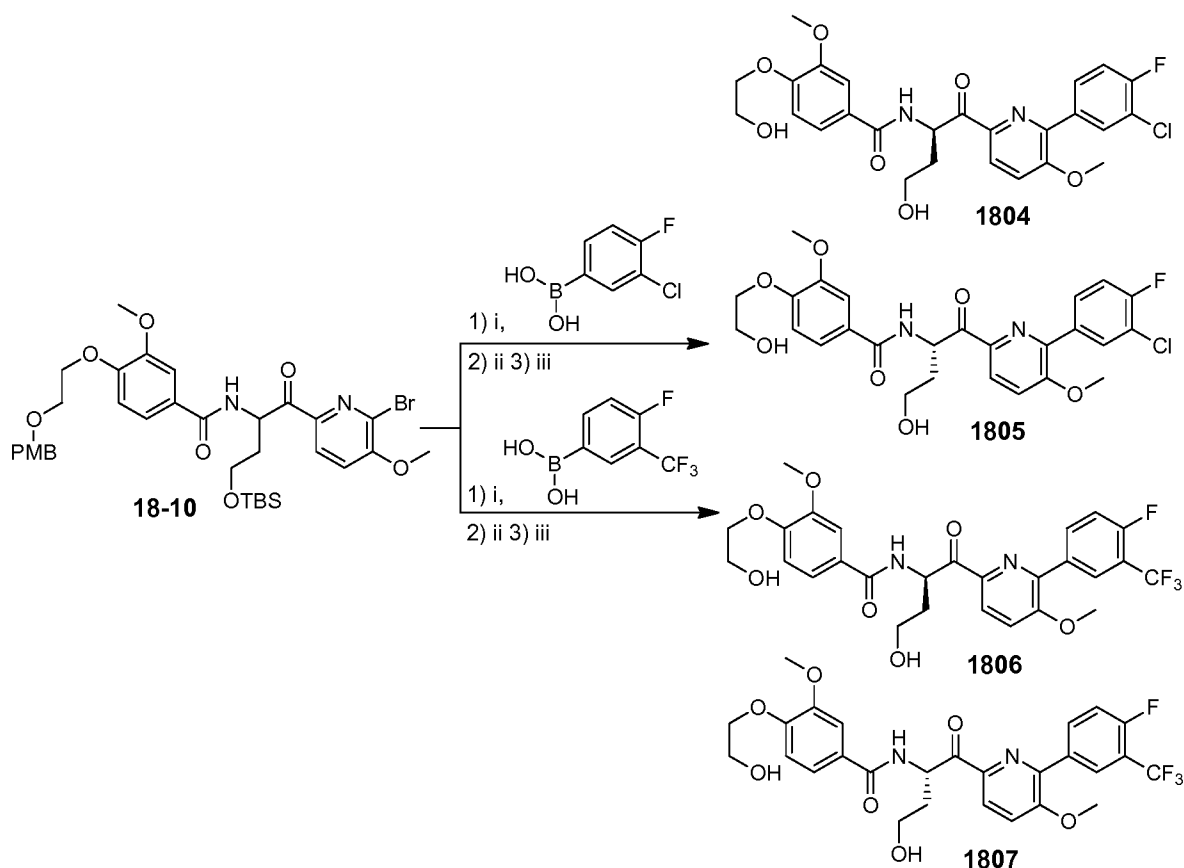
[0984] A 2M *i*-PrMgCl solution in THF (710 uL, 1.42 mmol) was added to a solution of **15-1** (209 mg, 0.670 mmol) and **18-9** (263 mg) in dry THF (4mL). The mixture was stirred at rt for 15 mins. Methanol and water were added, and the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc. The organic portion was washed twice with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 70:30 to 50:50) afforded **18-10** as an off-white solid (206 mg, 19% over four steps). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.01, 0.02 (2 x s, 6 H), 0.84 (s, 9 H), 2.37 (d, *J*=5.5 Hz, 2 H), 3.75 -3.84 (m, 5 H), 3.87 (t, *J*=5.1 Hz, 2 H), 3.93 (s, 3 H), 4.01 (s, 3 H), 4.25 (t, *J*=5.1 Hz, 2 H), 4.59 (s, 2 H), 5.95 (d, *J*=5.3 Hz, 1 H), 6.84 -6.95 (m, 3 H), 7.24 (d, *J*=8.5 Hz, 1 H), 7.31 (d, *J*=8.5 Hz, 2 H), 7.36 (dd, *J*=8.4, 1.9 Hz, 1 H), 7.47 (d, *J*=1.8 Hz, 1 H), 7.58 (d, *J*=6.5 Hz, 1 H), 8.08 (d, *J*=8.5 Hz, 1 H).

[0985] A mixture of **18-10** (74.0 mg, 0.104 mmol), (3-chloro-4-fluorophenyl)boronic acid (45.0 mg, 0.260 mmol), Pd(dppf)Cl₂ (4.0 mg, 0.005 mmol) and aq Na₂CO₃ (2M solution, 75 uL, 0.150 mmol) in DCE (5 mL) was degassed and stirred with heat at 85°C for 1 h. Water and DCM were added. The layers were separated and the organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 60:40) afforded **18-11** as an off-white solid. UPLC/MS(ES⁺), *m/z*: 789.27 [M+H]⁺.

[0986] Trifluoroacetic acid (100 μ L) was added to a solution of **18-11** in DCM (7 mL). The mixture was stirred at rt for 1 h, and then diluted with DCM. The organic portion was washed with 1M aq NaOH solution and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by reverse column chromatography (water- CH_3CN , 100:0 to 35:65) to afford compound **1802** as a white solid (7 mg, 12% over two steps). UPLC/MS(ES^+), m/z : 555.20 $[\text{M}+\text{H}]^+$.



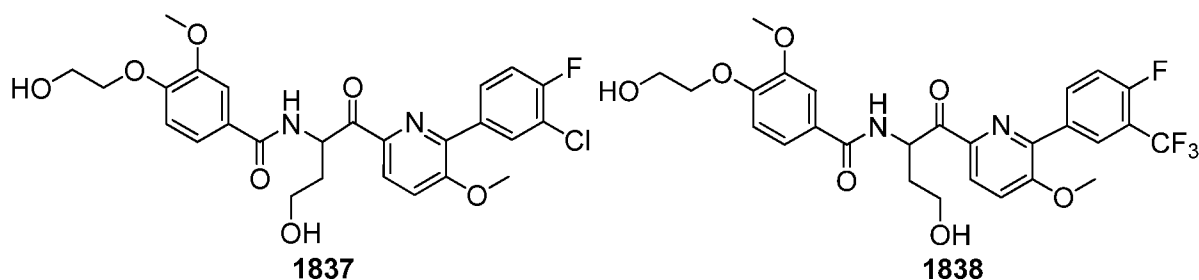
[0987] Synthesis performed using L-homoserine lactone hydrochloride as a starting material afforded compound **1803** as a single enantiomer (*S*, er > 98:2, t_R 22.1 min, [Chiralpak IB column (25 x 2.0 cm, 5 μ M), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 75/25% v/v, flow rate: 0.8 mL/min, UV detection DAD 220 nm]). UPLC and ^1H NMR analyses of compound **1803** were identical to those for compound **1802**.

EXAMPLE 18-4**Preparation of Compounds 1804, 1805, 1806 and 1807**

[0988] Suzuki coupling of **18-10** with (3-chloro-4-fluorophenyl)boronic acid followed by removal of all the protecting groups (TFA-DCM) afforded a mixture of compounds **1804** and **1805** (27% over two steps). This mixture of compounds (42 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column (25 x 2.0 cm, 5 μ M), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 75/25% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm] to obtain compound **1804** (15 mg, enantiomer 1 (*R*), t_R 13.3 min) and compound **1805** (12 mg, enantiomer 2 (*S*), t_R 15.3 min) based on the order of elution. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES^+), m/z : 533.32 [$\text{M}+\text{H}$] $^+$.

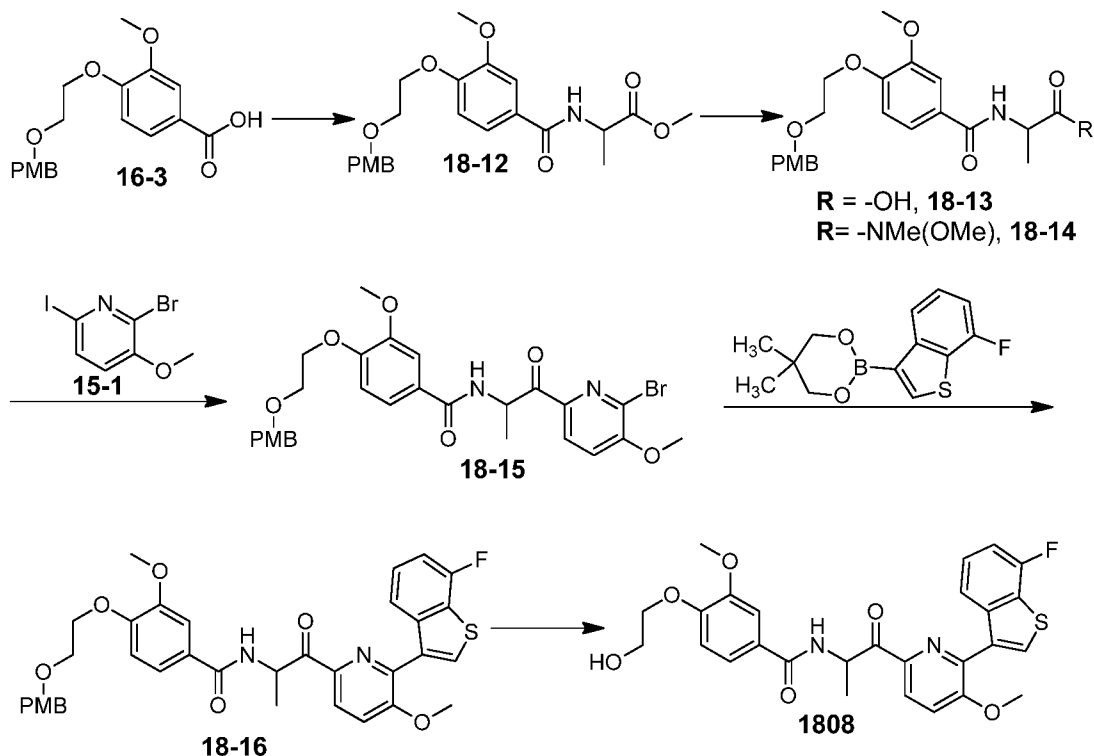
[0989] Suzuki coupling of **18-10** with [4-fluoro-3-(trifluoromethyl)phenyl]boronic acid followed by removal of all the protecting groups (TFA-DCM) afforded a mixture of compounds **1806** and **1807** (46% over two steps). This mixture of compounds (54 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column

(25 x 2.0 cm, 5 μ M), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 72/28% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm] to obtain compound **1806** (23 mg, enantiomer 1 (*R*), t_R 12.2 min) and compound **1807** (27 mg, enantiomer 2 (*S*), t_R 14.7 min) based on the order of elution. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES^+), m/z : 566.92 $[\text{M}+\text{H}]^+$.



[0990] Compounds **1837** and **1838** were obtained as described above in Example 18-4.

EXAMPLE 18-5
Preparation of Compound 1808



[0991] 4-Methylmorpholine (1.23 mL, 11.2 mmol) was added to a mixture of 2-chloro-4,6-dimethoxy-1,3,5-triazine (862 mg, 4.91 mmol) and **16-3** (1.12 g, 3.51 mmol) in CH₃CN (20mL). The mixture was stirred at rt for 1 h. (DL)-Alanine methyl ester

hydrochloride (764 mg, 5.49 mmol) was added, and the mixture was stirred at rt for an additional 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc, and the organic portion was washed with 1M aq HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Crude **18-12** (1.43 g) was used in the next step without further purification. UPLC/MS(ES^+), m/z : 418.20 $[\text{M}+\text{H}]^+$.

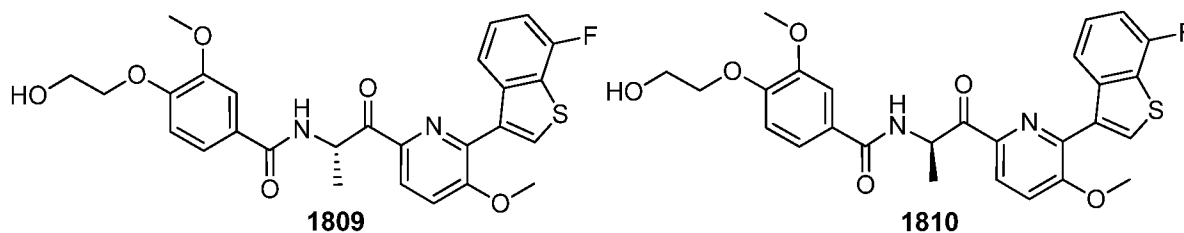
[0992] Amide **18-12** (1.43 g) was dissolved in a 2:1:1 THF-MeOH- H_2O mixture (12 mL) and treated with LiOH- H_2O (617 mg, 10.3 mmol). After 1 h, the volatiles were removed under reduced pressure. The residue was partitioned between DCM and 1M aq HCl solution, and the layers were separated. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **18-13** (1.10 g). UPLC/MS(ES^+), m/z : 404.20 $[\text{M}+\text{H}]^+$.

[0993] A mixture of **18-13** (1.10 g, 2.71 mmol), HOBt (660 mg, 4.88 mmol), EDC (727 mg, 3.79 mmol), TEA (680 μL , 4.88 mmol) and *N,O*-Dimethylhydroxylamine hydrochloride (396 mg, 4.06 mmol) in DCM (22 mL) was stirred at rt for 18 h. A 1M aq HCl solution was added and the mixture was stirred at rt for 10 mins. The mixture was filtered from the precipitate and the phases were separated. The organic portion was washed with 1M aq HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 90:10) afforded **18-14** (919 mg, 76%). UPLC/MS(ES^+), m/z : 447.20 $[\text{M}+\text{H}]^+$.

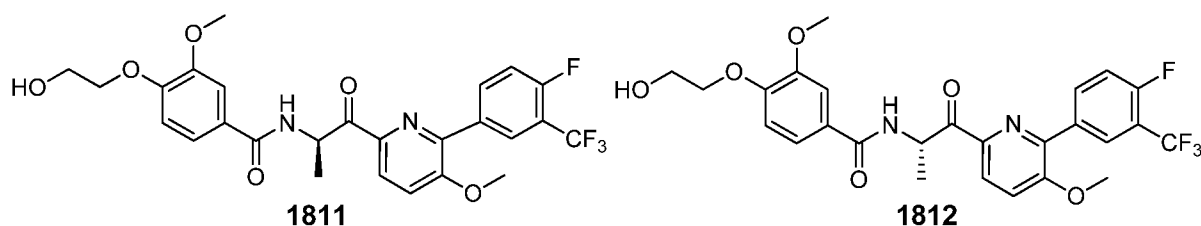
[0994] A 2M *i*-PrMgCl solution in THF (840 μL , 1.68 mmol) was added to a solution of **15-1** (313 mg, 1.00 mmol) and **18-14** (300 mg, 0.607 mmol) in dry THF (6 mL). The mixture was stirred at rt for 45 mins. Methanol and water were added, and the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and the organic portion was washed twice with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 70:30 to 0:100) afforded **18-15** as a yellow solid (240 mg, 63%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.62 (d, $J=7.3$ Hz, 3 H), 3.83 (s, 3 H), 3.86 -3.91 (m, 2 H), 3.95 (s, 3 H), 4.03 (s, 3 H), 4.26 (t, $J=5.1$ Hz, 2 H), 4.60 (s, 2 H), 5.99 (t, $J=7.1$ Hz, 1 H), 6.85 -6.97 (m, 3 H), 7.17 (d, $J=7.3$ Hz, 1 H), 7.26 (d, $J=8.5$ Hz, 1 H), 7.31 (d, $J=8.5$ Hz, 2 H), 7.38 (dd, $J=8.3$, 2.0 Hz, 1 H), 7.45 -7.51 (m, 1 H), 8.11 (d, $J=8.3$ Hz, 1 H).

[0995] A mixture of **18-15** (240 mg, 0.420 mmol), 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (280 mg, 1.05 mmol), Pd(dppf)Cl₂ (22.0 mg, 0.029 mmol) and aq Na₂CO₃ (2M solution, 360 uL, 1.26 mmol) in DCE (2 mL) was degassed and stirred with heat at 85°C for 1 h. Water and DCM were added. The mixture was filtered from the solids, and the layers were separated. The organic phase was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-16** was used in the next step without further purification.

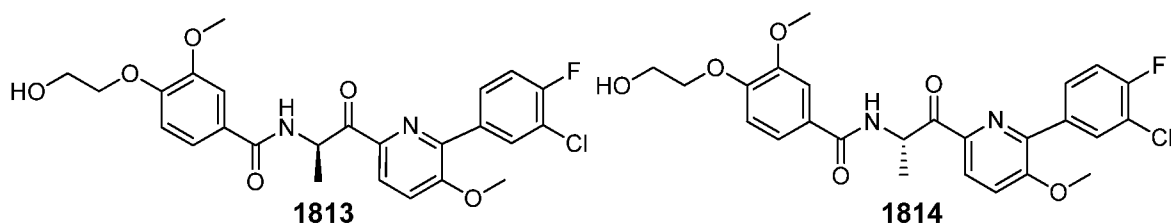
[0996] PMB-ether **18-16** was dissolved in a 1:1 DCM-TFA solution (3.4 mL). The mixture was stirred at rt for 1 h, then diluted with DCM and neutralized with saturated aq Na₂CO₃ solution. The aqueous phase was extracted with DCM. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 85:15) followed by trituration of the collected fractions with a CH₃CN-EtOAc-cyclohexane mixture afforded compound **1808** as a white solid (56.0 mg, 26% over two steps). UPLC/MS(ES⁺), m/z: 525.20 [M+H]⁺.



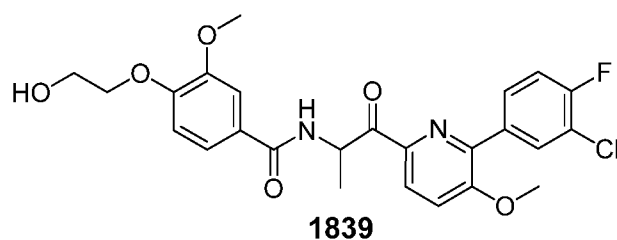
[0997] Compounds **1809** and **1810** were prepared starting from enantiomerically pure (L)-alanine methyl ester hydrochloride by following a synthetic route, which closely follows that described for preparation of compound **1808**. An unequal mixture of enantiomers was obtained. This mixture of compounds (92 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column (25 x 2.0 cm, 5 uM), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 75/25% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm] to obtain compound **1809** (13.2 mg, enantiomer 1 (*R*), t_R 16.8 min) and compound **1810** (38.0 mg, enantiomer 2 (*S*), t_R 18.1 min) based on the order of elution. UPLC and ¹H NMR analyses for the two enantiomers were superimposable and identical to those for compound **1808**.



[0998] Suzuki coupling of **18-15** (prepared starting from (L)-alanine methyl ester hydrochloride) with [4-fluoro-3-(trifluoromethyl)phenyl]boronic acid followed by PMB-group removal afforded a mixture of compounds **1811** and **1812** (er 6.2:93.8, 22% over two steps). This mixture of compounds (52 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column (25 x 2.0 cm, 5 μ M), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 70/30% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm] to obtain to obtain compound **1811** (2.4 mg, enantiomer 1 (*R*), t_R 11.1 min) and compound **1812** (38.0 mg, enantiomer 2 (*S*), t_R 12.7 min) based on the order of elution. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES^+), m/z : 537.21 [$M+H$] $^+$.

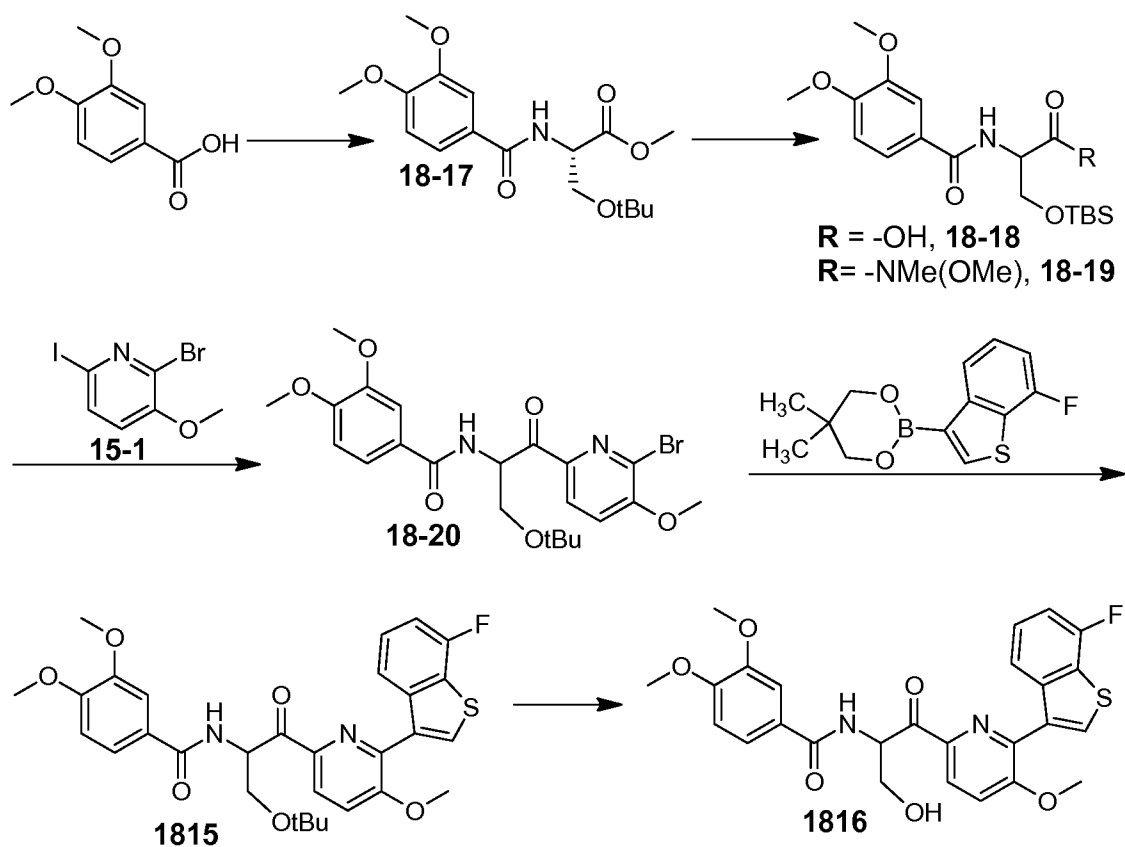


[0999] Suzuki coupling of **18-15** (prepared starting from (L)-alanine methyl ester hydrochloride) with (3-chloro-4-fluorophenyl)boronic acid followed by PMB-group removal afforded a mixture of compounds **1813** and **1814** (er 26:74, 40% over two steps). This mixture of compounds (86 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column (25 x 2.0 cm, 5 μ M), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 70/30% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm] to obtain compound **1813** (15.6 mg, enantiomer 1 (*R*), t_R 11.1 min) and compound **1814** (24.0 mg, enantiomer 2 (*S*), t_R 12.7 min) based on the order of elution. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.49 (d, $J=7.3$ Hz, 3 H), 3.74 (q, $J=5.2$ Hz, 2 H), 3.81 (s, 3 H), 3.97 -4.10 (m, 5 H), 4.89 (t, $J=5.4$ Hz, 1 H), 5.89 (t, $J=7.0$ Hz, 1 H), 7.03 (d, $J=8.3$ Hz, 1 H), 7.48 (d, $J=1.8$ Hz, 1 H), 7.50 -7.56 (m, 1 H), 7.57 -7.62 (m, 1 H), 7.80 (d, $J=8.8$ Hz, 1 H), 7.99 -8.09 (m, 2 H), 8.18 (dd, $J=7.4, 2.1$ Hz, 1 H), 8.66 (d, $J=6.8$ Hz, 1 H). UPLC/MS(ES^+), m/z : 503.18 [$M+H$] $^+$.



[1000] Compound **1839** was obtained as described herein for the preparation for compounds **1813** and **1814**.

EXAMPLE 18-6
Preparation of Compounds 1815 and 1816



[1001] 4-Methylmorpholine (900 μ L, 8.22 mmol) was added to a mixture of 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.34 g, 7.66 mmol) and 3,4-dimethoxybenzoic acid (1.00 g, 5.48 mmol) in CH_3CN (30 mL). The mixture was stirred at rt for 30 mins, then *O*-*tert*-butyl-L-serine methyl ester hydrochloride (1.50 g, 7.12 mmol) was added. The mixture was stirred at rt for 1 h. The volatiles were removed under reduced pressure, and the residue was dissolved in EtOAc. The organic portion was washed twice with 1M aq HCl solution,

dried (Na_2SO_4), filtered and concentrated under reduced pressure. Crude **18-17** was used in the next step without further purification. UPLC/MS(ES^+), m/z : 340.20 $[\text{M}+\text{H}]^+$.

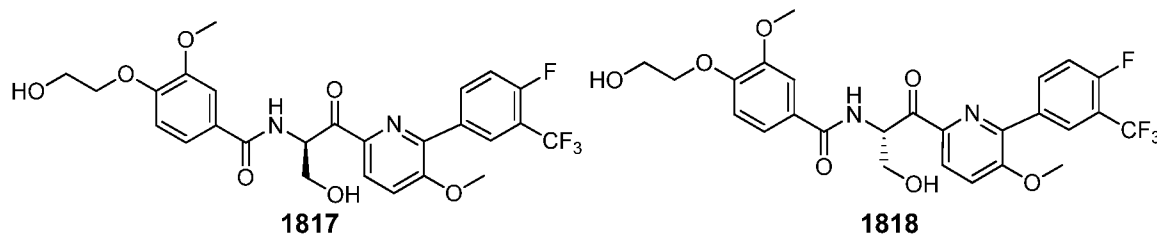
[1002] Amide **18-17** was dissolved in a 2:1:1 THF-MeOH- H_2O mixture (20 mL) and treated with LiOH- H_2O (690 mg, 16.4 mmol). After 30 mins, the volatiles were removed under reduced pressure. The residue was partitioned between DCM and 1M aq HCl solution, and the layers were separated. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **18-18**. UPLC/MS(ES^+), m/z : 326.10 $[\text{M}+\text{H}]^+$.

[1003] A mixture of **18-18**, HOBT (1.33 g, 9.86 mmol), EDC (1.47 g, 7.67 mmol), TEA (1.37 mL, 9.86 mmol) and *N,O*-Dimethylhydroxylamine hydrochloride (801 mg, 8.22 mmol) in DCM (20 mL) was stirred at rt for 18 h. A 1M aq HCl solution was added, and the mixture was stirred at rt for 10 mins. The mixture was filtered from the precipitate and the phases were separated. The organic portion was washed with 1M aq HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 20:80) afforded **18-19** (1.70, 84% over three steps). UPLC/MS(ES^+), m/z : 369.24 $[\text{M}+\text{H}]^+$.

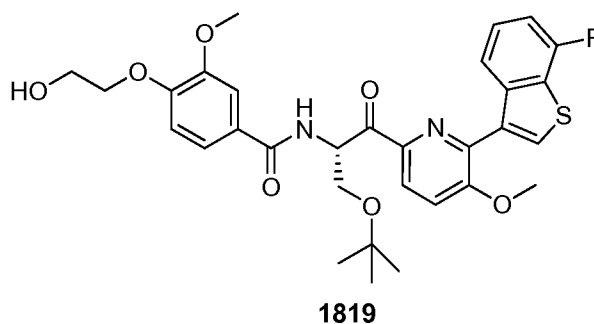
[1004] A 2M *i*-PrMgCl solution in THF (2.3 mL, 4.60 mmol) was added to a solution of **15-1** (1.08 g, 3.45 mmol) and **18-19** (850 mg, 2.30 mmol) in dry THF (20 mL). The mixture was stirred at rt. After 30 min, additional *i*-PrMgCl solution (1.67 mL, 3.45 mmol) was added and stirring was continued for 15 mins. The reaction was quenched with a saturated aq NH_4Cl solution. The aqueous portion was extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 20:80) afforded **18-20** as a yellow solid (525 mg, 46%). UPLC/MS(ES^+), m/z : 495.15 $[\text{M}+\text{H}]^+$.

[1005] A mixture of **18-20** (200 mg, 0.404 mmol), 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (212 mg, 0.806 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (15 mg, 0.020 mmol) and aq Na_2CO_3 (2M solution, 606 μL , 1.21 mmol) in DCE (4 mL) was degassed and stirred with heat at 85°C for 3 h. Water and DCM were added, and the layers were separated. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 50:50) afforded compound **1815** (181 mg, 79%). UPLC/MS(ES^+), m/z : 567.26 $[\text{M}+\text{H}]^+$.

[1006] Compound **1815** (135 mg, 0.238 mmol) was dissolved in a 10:1 DCM-TFA solution (4.4 mL). The mixture was stirred at rt for 7 h, then diluted with DCM and washed with 2M aq NaOH solution. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (water-CH₃CN, 95:5 to 0:100) to afford compound **1816** as a white solid (29 mg, 24%). UPLC/MS(ES⁺), m/z: 511.17 [M+H]⁺.

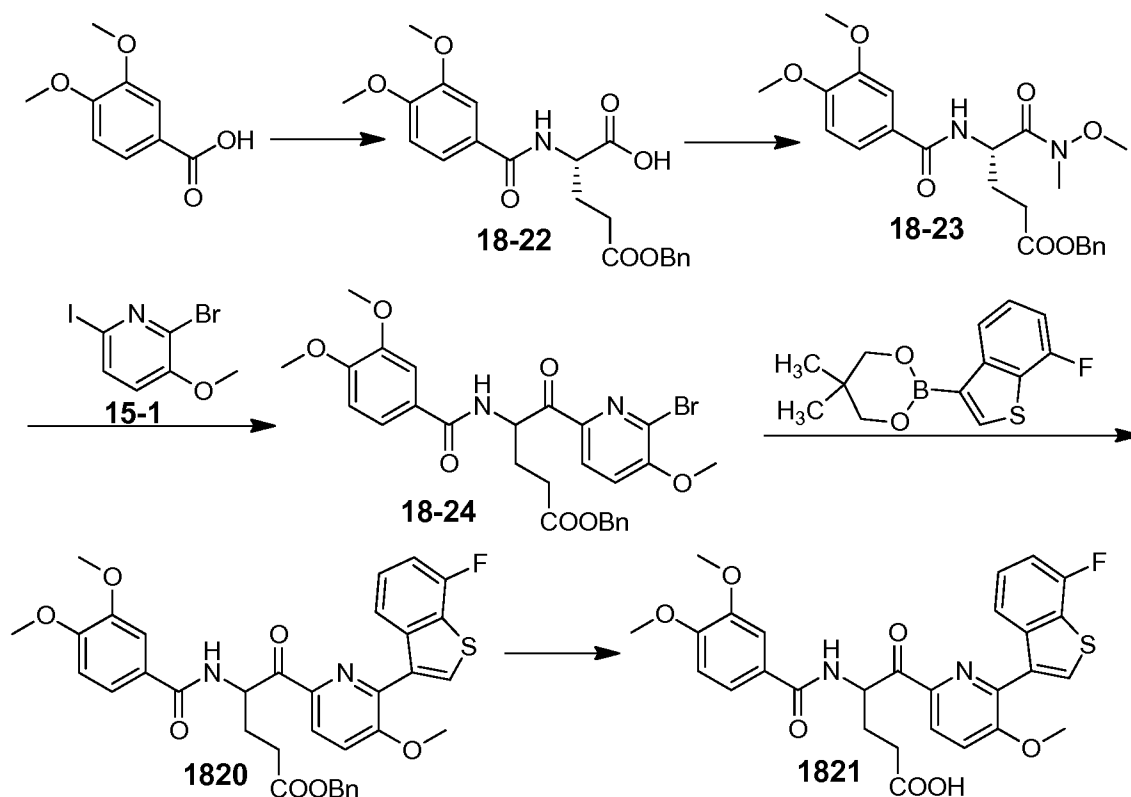


[1007] Compounds **1817** and **1818** were prepared starting from **16-3** by following a synthetic route, which closely follows that described for preparation of compound **1815**. Coupling of **E-21** with [4-fluoro-3-(trifluoromethyl)phenyl]boronic acid followed by removal of the PMB-group (TFA-DCM) afforded a mixture of compounds **1817** and **1818**. This mixture of compounds (51 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column (25 x 2.0 cm, 5 μ M), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 70/30% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm] to obtain compound **1817** (11.8 mg, enantiomer 1 (*R*), t_R 12.9 min) and compound **1818** (10.0 mg, enantiomer 2 (*S*), t_R 14.6 min) based on the order of elution. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES^+), m/z : 553.20 $[\text{M}+\text{H}]^+$.



[1008] Coupling of **18-21** with 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane followed by removal of the PMB-group by treatment with TFA afforded compound **1819** as a white solid. UPLC/MS(ES⁺), m/z: 597.30 [M+H]⁺.

EXAMPLE 18-7
Preparation of Compounds 1820 and 1821



[1009] Thionyl chloride (2.0 mL, 27.5 mmol) was added to a mixture of 3,4-dimethoxybenzoic acid (1.00 g, 5.49 mmol) in toluene (8 mL). The mixture was stirred with heat to 120 °C for 18 h. The volatiles were removed under reduced pressure. The residue was dissolved in DCM (2 mL), and the solution was added to a mixture of (2S)-2-amino-5-(benzyloxy)-5-oxopentanoic acid (780 mg, 3.29 mmol) and TEA (2.29 mL, 16.5 mmol) in DCM (6 mL). After 1 h, the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **18-22** (887 mg, 67%). UPLC/MS(ES⁺), m/z: 402.20 [M+H]⁺.

[1010] 4-Methylmorpholine (631 uL, 5.74 mmol) was added to a mixture of 2-chloro-4,6-dimethoxy-1,3,5-triazine (542 mg, 3.09 mmol) and **18-22** (887 mg, 1.12 mmol) in CH₃CN (6 mL). The mixture was stirred at rt for 1 h. *N,O*-Dimethylhydroxylamine hydrochloride (278 mg, 2.87 mmol) was added, and the mixture was left to stir at rt for 1 h. The volatiles were removed under reduced pressure. Chromatography of the residue

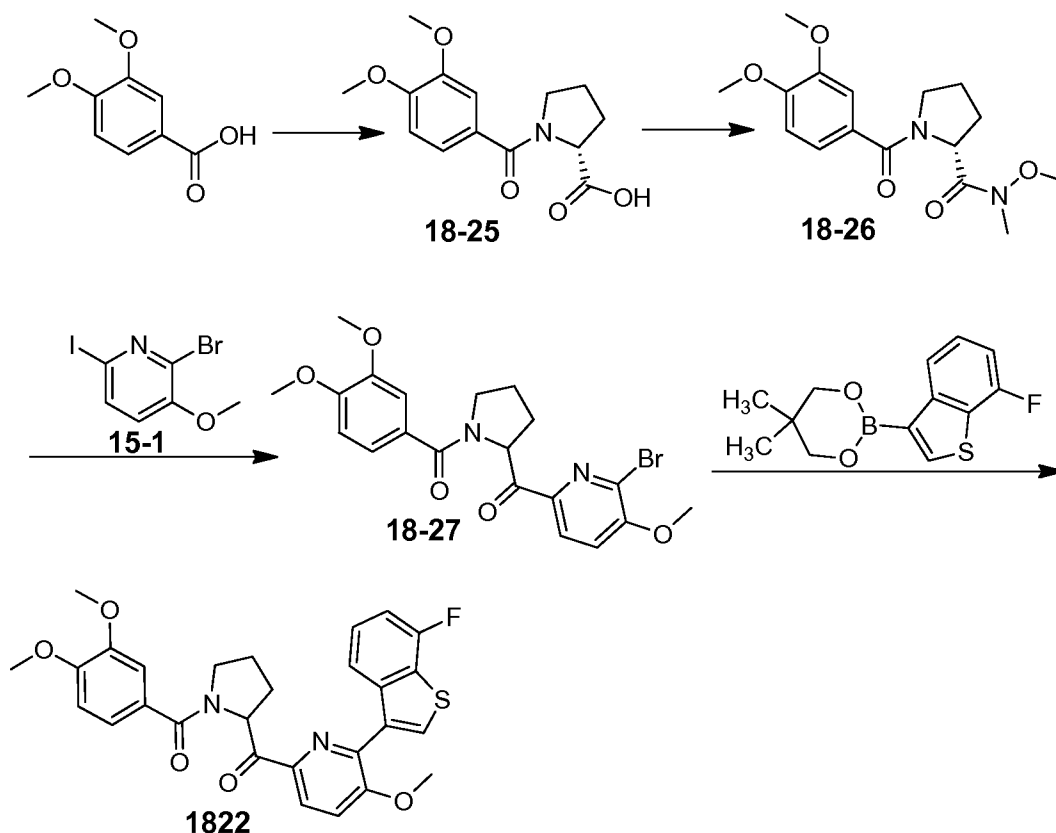
(cyclohexane-EtOAc, 100:0 to 0:100) afforded **18-23** as a pale yellow wax (308 mg, 62%). UPLC/MS(ES^+), m/z : 445.20 $[\text{M}+\text{H}]^+$.

[1011] A 2M *i*-PrMgCl solution in THF (862 μL , 1.72 mmol) was added to a solution of **15-1** (323 mg, 1.03 mmol) and **18-23** (308 mg, 0.69 mmol) in dry THF (6 mL). The mixture was stirred at rt for 20 mins and then quenched with 2M aq HCl solution. The aqueous portion was extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 20:80) afforded **18-24** as a pale yellow solid (100 mg, 25%). UPLC/MS(ES^+), m/z : 571.12 $[\text{M}+\text{H}]^+$.

[1012] A mixture of **18-24** (100 mg, 0.175 mmol), 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (115 mg, 0.437 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (9 mg, 0.012 mmol) and aq Na_2CO_3 (2M solution, 262 μL , 0.525 mmol) in DCE (3 mL) was degassed and stirred with heat at 85°C for 3 h. Chromatography of the mixture (cyclohexane-EtOAc, 90:10 to 0:100) afforded compound **1820** (109 mg). UPLC/MS(ES^+), m/z : 643.20 $[\text{M}+\text{H}]^+$.

[1013] A solution of compound **1820** (57.0 mg, 0.089 mmol) in DCM (2 mL) was treated with a 33% HBr solution in acetic acid (700 μL). After 2 h stirring at rt, saturated aq NaHCO_3 solution was added. The layers were separated and the aqueous portion was extracted with DCM. The combined organic portions were dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 70:30) afforded compound **1821** as a white solid (21 mg, 43%). UPLC/MS(ES^+), m/z : 553.10 $[\text{M}+\text{H}]^+$.

EXAMPLE 18-8
Preparation of Compound 1822



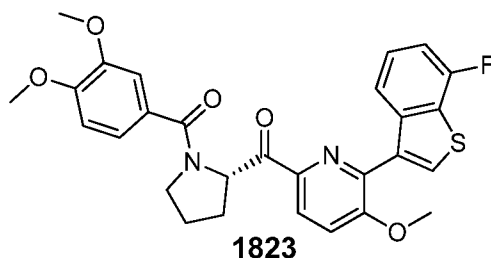
[1014] 4-Methylmorpholine (610 μ L, 4.38 mmol) was added to a mixture of 2-chloro-4,6-dimethoxy-1,3,5-triazine (672 mg, 3.83 mmol) and 3,4-dimethoxybenzoic acid (500 mg, 2.74 mmol) in CH_3CN (14 mL). The mixture was stirred at rt for 1 h, then D-proline (706 mg, 4.38 mmol) was added. The mixture was left to stir at rt for 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and washed with 1M aq HCl solution. The organic portion was (Na_2SO_4), filtered and concentrated under reduced pressure to afford **18-25** as a white solid (1.01 g). UPLC/MS(ES^+), m/z : 280.09 $[\text{M}+\text{H}]^+$.

[1015] A mixture of **18-25** (1.01 g), HOBT (875 mg, 6.48 mmol), EDC (966 mg, 5.04 mmol), TEA (903 μ L, 46.5 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (526 mg, 5.40 mmol) in DCM (30 mL) was stirred at rt overnight. A 1M aq HCl solution was added and the mixture was stirred at rt for 10 mins. The mixture was filtered from the solids and the layers were separated. The organic portion was washed with 1M aq HCl solution,

dried (Na_2SO_4), filtered and concentrated under reduced pressure. Crude **18-26** (1.07 g) was used in the next step without further purification. UPLC/MS(ES^+), m/z : 323.14 $[\text{M}+\text{H}]^+$.

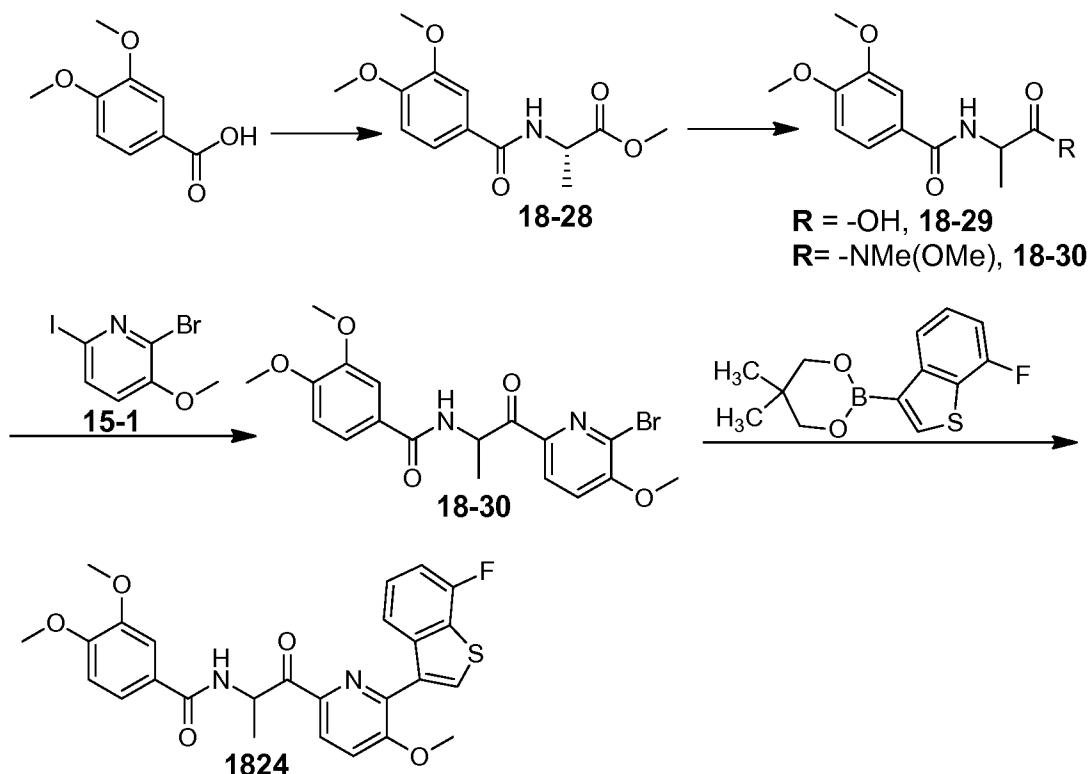
[1016] A 2M *i*-PrMgCl solution in THF (3.80 mL, 7.75 mmol) was added to a solution of **15-1** (1.40 g, 4.65 mmol) and **18-26** (1.0 g, 3.10 mmol) in dry THF (10 mL). The mixture was stirred at rt for 30 mins and then quenched with a 1M aq HCl solution. The aqueous portion was extracted with EtOAc. The combined organic portions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc) afforded **18-27** as an off-white solid (214 mg, 17% over three steps). UPLC/MS(ES^+), m/z : 449.07 $[\text{M}+\text{H}]^+$.

[1017] A mixture of **18-27** (100 mg, 0.220 mmol), 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (145 mg, 0.550 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (8 mg, 0.011 mmol) and aq Na_2CO_3 (2M solution, 165 μL , 0.330 mmol) in DCE (2 mL) was degassed and stirred with heat at 85°C for 3 h. Water and DCM were added, and the layers were separated. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the mixture (cyclohexane-EtOAc, 20:80 to 0:100) afforded compound **1822** (20 mg, 17%). UPLC/MS(ES^+), m/z : 521.15 $[\text{M}+\text{H}]^+$.



[1018] Compound **1823** was prepared starting from L-proline by following a synthetic route, which closely follows that described for preparation of compound **1822**. UPLC/MS(ES^+), m/z : 521.15 $[\text{M}+\text{H}]^+$.

EXAMPLE 18-9
Preparation of Compound 1824



[1019] A mixture of 3,4-dimethoxybenzoic acid (700 mg, 3.84 mmol), HOBT (934 mg, 6.91 mmol), EDC (1.03 g, 5.38 mmol), methyl (2S)-2-aminopropanoate hydrochloride (804 mg, 5.76 mmol) and TEA (1.50 mL, 10.8 mmol) in DCM (17 mL) was stirred at rt for 2 h. A 1M aq HCl solution was added and the mixture was stirred until a white solid precipitated. The mixture was filtered from the solids and the layers separated. The organic portion was washed with 1M aq HCl solution, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-28** (1.03 g) was used in the next step. UPLC/MS(ES⁺), m/z: 268.11 [M+H]⁺.

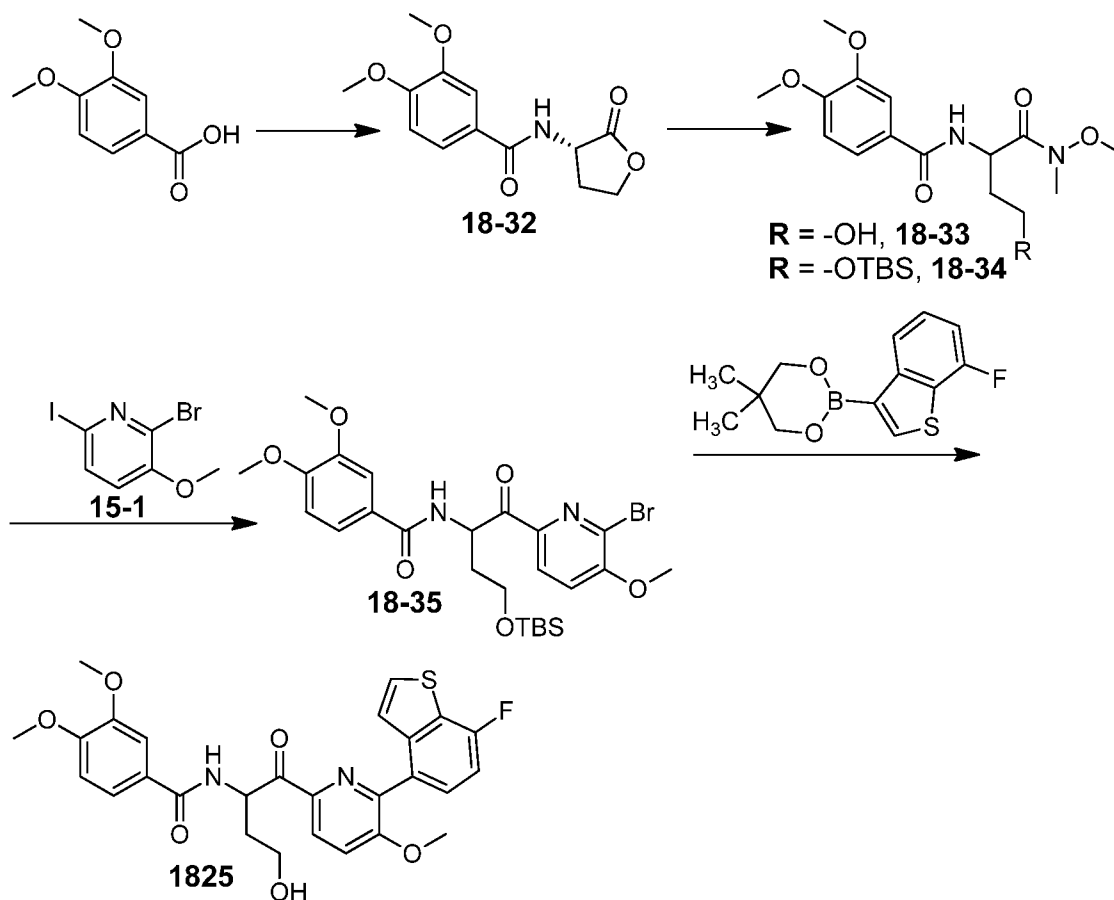
[1020] Amide **18-28** (1.03 g) was dissolved in a 4:2:1 THF-MeOH-H₂O mixture (17.5 mL) and treated with LiOH-H₂O (461 mg, 9.60 mmol). After 30 mins, the volatiles were removed under reduced pressure. The residue was partitioned between EtOAc and 1M aq HCl solution, and the layers were separated. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford **18-29** (909 mg). UPLC/MS(ES⁺), m/z: 254.09 [M+H]⁺.

[1021] A mixture of **18-29** (900 mg), HOBT (865 mg, 6.40 mmol), EDC (744 mg, 7.63 mmol), TEA (1.39 mL, 9.96 mmol) and *N,O*-Dimethylhydroxylamine hydrochloride (744 mg, 7.63 mmol) in DCM (20 mL) was stirred at rt for 1 h. vA 1M aq HCl solution was added and the mixture was stirred at rt for 10 mins. The mixture was filtered from the precipitate and the phases were separated. The organic portion was washed with 1M aq HCl solution, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-30** (914 mg) was used in the next step without further purification. UPLC/MS(ES⁺), m/z: 297.10 [M+H]⁺.

[1022] A 2M *i*-PrMgCl solution in THF (6.35 mL, 12.7 mmol) was added dropwise to a solution of **15-1** (2.0 g, 6.37 mmol) in dry THF (10 mL). After 40 mins, a Grignard reagent was added to a solution of **18-30** (1.20 g, 4.26 mmol) in THF (10 mL), which had been pre-heated to 40°C. The mixture was stirred at 40°C for 1 h. The mixture was partitioned between saturated aq NH₄Cl solution and EtOAc, and the layers were separated. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **18-31**.

[1023] A mixture of **18-31**, 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (86 mg, 0.325 mmol), Pd(dppf)Cl₂ (21.6 mg, 0.030 mmol) and KF (69.0 mg, 1.18 mmol) in DMF (4mL) was degassed and stirred with heat at 85°C for 4 h. The mixture was diluted with water and extracted three times with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) followed by trituration of the collected fractions with MeOH afforded compound **1824** as a white solid (35 mg). UPLC/MS(ES⁺), m/z: 495.14 [M+H]⁺.

EXAMPLE 18-10
Preparation of Compound 1825



[1024] A mixture of 3,4-dimethoxybenzoic acid (500 mg, 2.74 mmol), NMM (452 μ L, 4.12 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (671 mg, 3.84 mmol) in CH_3CN (10 mL) was stirred at rt for 30 mins. A mixture of (3S)-3-aminooxolan-2-one hydrochloride (484 mg, 3.56 mmol) and NMM (391 μ L, 3.56 mmol) in CH_3CN -DMF (2:1, 3 mL) was added and the mixture was stirred at rt for 1.5 h. The volatiles were removed under reduced pressure and the residue was dissolved in EtOAc. The organic portion was washed with 1M aq HCl and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Crude **18-32** (1.0 g) was used in the next step without further purification. UPLC/MS(ES^+), m/z : 266.10 $[\text{M}+\text{H}]^+$.

[1025] Pyridine (301 μ L, 3.73 mmol) and AlMe_3 (2M solution in heptanes, 2.52 mL, 5.07 mmol) were added to a suspension of $\text{MeONHMe}\cdot\text{HCl}$ (492 mg, 5.07 mmol) in DCM (6 mL). After 15 mins, a solution of **18-32** (450 mg) in DCM (2 mL) was added dropwise. The mixture was stirred at rt for 18 h, then cooled to 0 $^\circ\text{C}$ and quenched with 1M

aq HCl solution. The organic portion was diluted with DCM and washed with 1M aq HCl solution and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-33** (310 mg) was used in the next step without further purification.

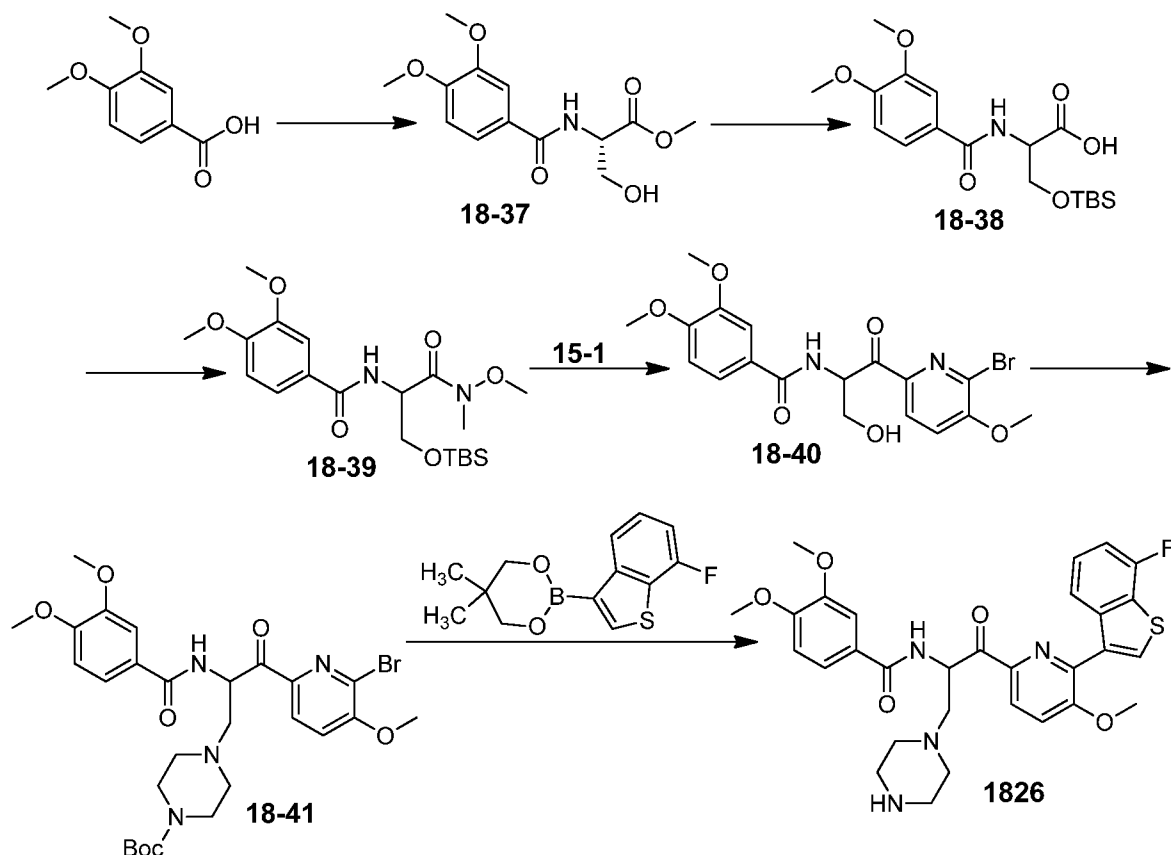
[1026] DIPEA (331 uL, 1.90 mmol) and TBSCl (214 mg, 1.42 mmol) were added to a solution of **18-33** (310 mg) in DCM. After 16 h at rt, the mixture was diluted with DCM and washed with water and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **18-34** (220 mg). UPLC/MS(ES⁺), m/z: 441.30 [M+H]⁺.

[1027] A 2M *i*-PrMgCl solution in THF (852 uL, 1.70 mmol) was added dropwise to a solution of **18-34** (300 mg, 0.682 mmol) and **15-1** (319 mg, 1.02 mmol) in dry THF (12 mL). The mixture was stirred at rt for 1 h and then quenched with 1M aq HCl solution. The aqueous portion was extracted with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-35** was used in the next step without further purification.

[1028] A 1M TBAF solution in THF (1.5 mL) was added to a stirred solution of **18-35** in THF (1.5 mL). After 2 h, the mixture was diluted with EtOAc and washed with water. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-36** (structure not shown) was used in the next step without further purification.

[1029] A mixture of **18-36**, 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (100 mg, 0.378 mmol), Pd(dppf)Cl₂ (10 mg, 0.014 mmol) and aq Na₂CO₃ (2M solution, 150 uL, 300 mmol) in DCE (2 mL) was degassed and stirred with heat at 85°C for 2 h. Water and DCM were added, and the layers were separated. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the mixture (EtOAc-MeOH, 100:0 to 95:5) afforded compound **1825** (25 mg, 7% over three steps). UPLC/MS(ES⁺), m/z: 525.15 [M+H]⁺.

EXAMPLE 18-11
Preparation of Compound 1826



[1030] 4-Methylmorpholine (1.80 mL, 16.9 mmol) was added to a mixture of 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.60 g, 9.10 mmol) and 3,4-dimethoxybenzoic acid (1.20 g, 6.50 mmol) in CH₃CN (35 mL). The mixture was stirred at rt for 1 h, then (DL)-serine methyl ester hydrochloride (1.60 g, 10.4 mmol) was added. The mixture was stirred at rt for 1 h. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and washed with 1M aq HCl solution. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude **18-37** (2.0 g).

[1031] A mixture of **18-37** (350 mg, 1.24 mmol), TBSCl (224 mg, 1.49 mmol) and TEA (258 μ L, 1.85 mmol) in DCM (7 mL) was stirred at rt for 20 h. The mixture was washed with water. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude TBS-protected alcohol, which was used in the next step. The crude TBS-protected alcohol was dissolved in a 2:1 THF-MeOH mixture (3 mL). A solution of LiOH-H₂O (156 mg, 3.72 mmol) in water (1 mL) was added and the mixture was

stirred at rt for 30 mins. The organic solvents were removed under reduced pressure. The aqueous portion was acidified with saturated aq NH_4Cl solution and extracted three times with DCM. The combined organic portions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford crude **18-38**, which was used in the next step without further purification. UPLC/MS(ES^+), m/z : 387.20 $[\text{M}+\text{H}]^+$.

[1032] A solution of **18-38**, EDC (357 mg, 1.86 mmol), HOBT (251 mg, 1.86 mmol), MeNHOMe $\cdot\text{HCl}$ (144 mg, 1.50 mmol) and TEA (345 μL , 2.48 mmol) in DCM (4 mL) was stirred at rt for 2 h. The mixture was diluted with DCM. The organic portion was washed twice with saturated aq NH_4Cl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude **18-39** (471 mg), which was used in the next step without further purification.

[1033] A 2M *i*-PrMgCl solution in THF (1.55 mL, 3.10 mmol) was added dropwise to a solution of **18-39** (471 mg) and **15-1** (580 mg, 1.86 mmol) in dry THF (5 mL). The mixture was stirred at rt for 10 mins, then further *i*-PrMgCl (500 μL) was added. After 10 mins, the reaction was quenched with saturated aq NH_4Cl solution and the aqueous portion was extracted with EtOAc. The combined organic portions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 70:30 to 0:100) afforded the desired TBS-protected alcohol as a pale yellow wax (305 mg, 57% over four steps). ^1H NMR (400 MHz, CDCl_3) δ ppm -0.05, -0.12 (2 x s, 6 H), 0.81 (s, 9 H), 3.95 -4.01 (m, 7 H), 4.05 (s, 3 H), 4.21 (dd, $J=10.5$, 3.3 Hz, 1 H), 4.42 (dd, $J=10.5$, 3.0 Hz, 1 H), 6.00 -6.08 (m, 1 H), 6.95 (d, $J=8.3$ Hz, 1 H), 7.24 -7.29 (m, 1 H), 7.37 (d, $J=7.5$ Hz, 1 H), 7.44 -7.53 (m, 2 H), 8.10 (d, $J=8.5$ Hz, 1 H).

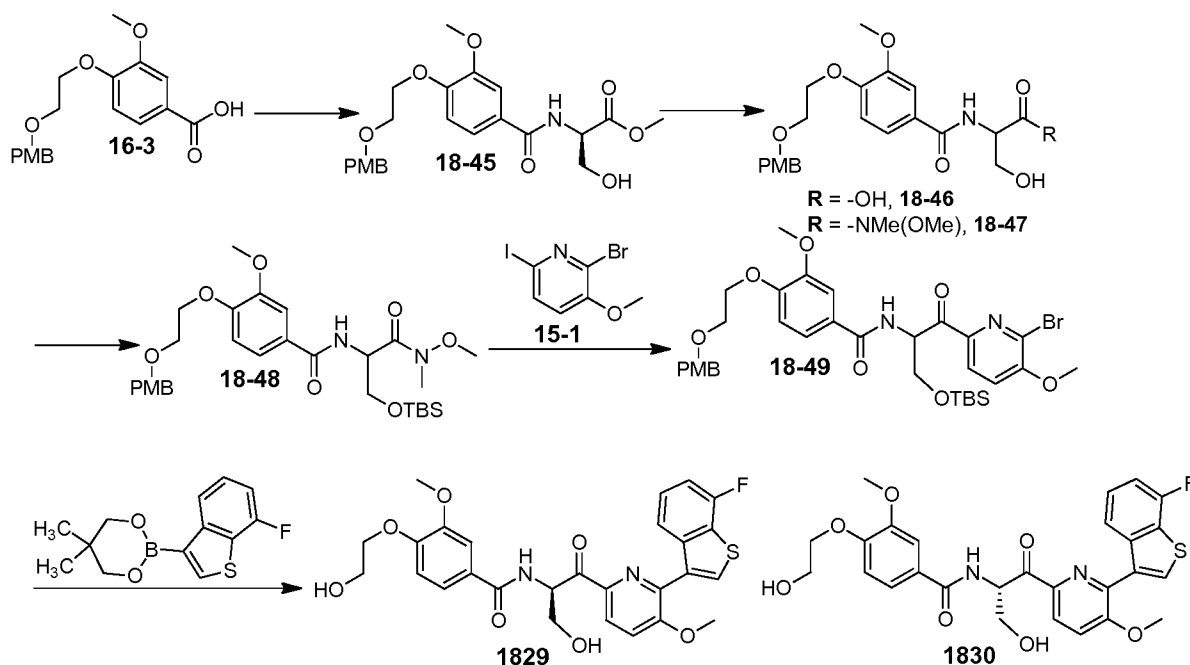
[1034] The TBS-protected alcohol was dissolved in THF (5 mL) and TBAF (1M solution in THF, 1.07 mL, 1.07 mmol) was added to the solution. After 45 mins, EtOAc was added. The organic portion was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Crude **18-40** was used in the next step without further purification. UPLC/MS(ES^+), m/z : 439.04 $[\text{M}+\text{H}]^+$.

[1035] A solution of **18-40**, MsCl (65 μL , 0.828 mmol) and TEA (115 μL , 0.828 mmol) in DCM (3 mL) was stirred at rt for 5 h. The volatiles were removed under reduced pressure. The residue was dissolved in TEA (1 mL) and 1-Boc piperazine (720 mg, 3.86

mmol) was added. The mixture was heated to 50°C and stirred for 18 h. The volatiles were removed under reduced pressure. Crude **18-41** was directly progressed to the next step.

[1036] A mixture of **18-41**, 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (100 mg, 0.378 mmol), Pd(dppf)Cl₂ (10 mg, 0.014 mmol) and aq Na₂CO₃ (2M solution, 150 uL, 300 mmol) in DCE (2 mL) was degassed and stirred with heat at 85°C for 2 h. Water and DCM were added, and the layers were separated. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the mixture (EtOAc-MeOH, 100:0 to 95:5) afforded the Boc-protected piperazine (55 mg, 15% overall yield). The Boc-protected piperazine (20 mg, 0.029 mmol) was dissolved in MeOH (2 mL) and treated with a 1M HCl solution in Et₂O (1 mL). The mixture was stirred at rt for 3 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water-CH₃CN, 100:0 to 0:100) to afford compound **1826** as an off-white solid (4 mg, 24%). UPLC/MS(ES⁺), m/z: 579.20 [M+H]⁺.

EXAMPLE 18-12 Preparation of Compounds 1829 and 1830



[1037] A mixture of acid **16-3** (1.00 g, 3.01 mmol), HOBT (732 mg, 5.42 mmol), EDC (807 mg, 4.21 mmol), TEA, 750 uL, 5.42 mmol) and D-serine methyl ester hydrochloride (700 mg, 4.51 mmol) in DCM (18 mL) was stirred at rt for 2 h. A 1M HCl

solution was added and the mixture was stirred at rt for 10 mins. The mixture was filtered from the solids and the layers were separated. The organic portion was washed with 1M aq HCl solution, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-45** was used the next step without further purification. UPLC/MS(ES⁺), m/z: 434.25 [M+H]⁺.

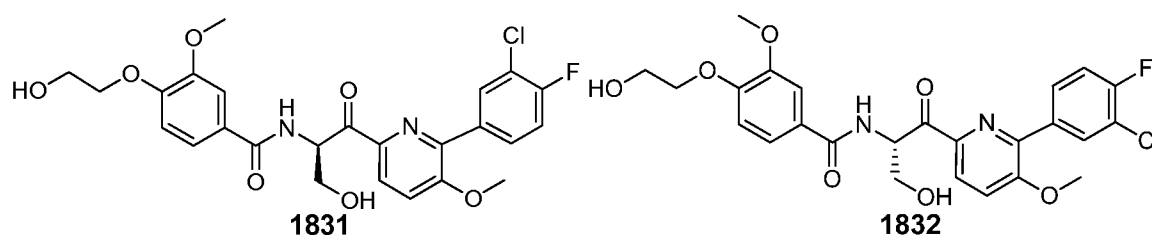
[1038] Amide **18-45** was dissolved in a 2:1:1 THF-MeOH-H₂O mixture (20 mL) and treated with LiOH-H₂O (379 mg, 9.03 mmol). After 30 mins, the volatiles were removed under reduced pressure. The residue was partitioned between DCM and 1M aq HCl solution. The layers were separated and the organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford **18-46** (1.13 g). UPLC/MS(ES⁺), m/z: 420.24 [M+H]⁺.

[1039] A mixture of **18-46** (1.13 g), HOBt (654 mg, 4.84 mmol), EDC (722 mg, 3.77 mmol), TEA (670 mL, 4.84 mmol) and *N,O*-Dimethylhydroxylamine hydrochloride (394 mg, 4.03 mmol) in DCM (16 mL) was stirred at rt for 1 h. A 1M aq HCl solution was added and the mixture was stirred at rt for 10 mins. The mixture was filtered from the precipitate and the phases were separated. The organic portion was washed with 1M aq HCl solution, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **18-47** (1.15 g) was used the next step without further purification. UPLC/MS(ES⁺), m/z: 463.20 [M+H]⁺.

[1040] A mixture of **18-47** (1.15 g), TEA (1.03 mL, 7.44 mmol) and TBSCl (744 mg, 4.96 mmol) in DCM (10 mL) was stirred at rt for 72 h. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 80:20 to 40:60) afforded **18-48** as a colourless oil (742 mg, 43% over four steps). UPLC/MS(ES⁺), m/z: 577.43 [M+H]⁺.

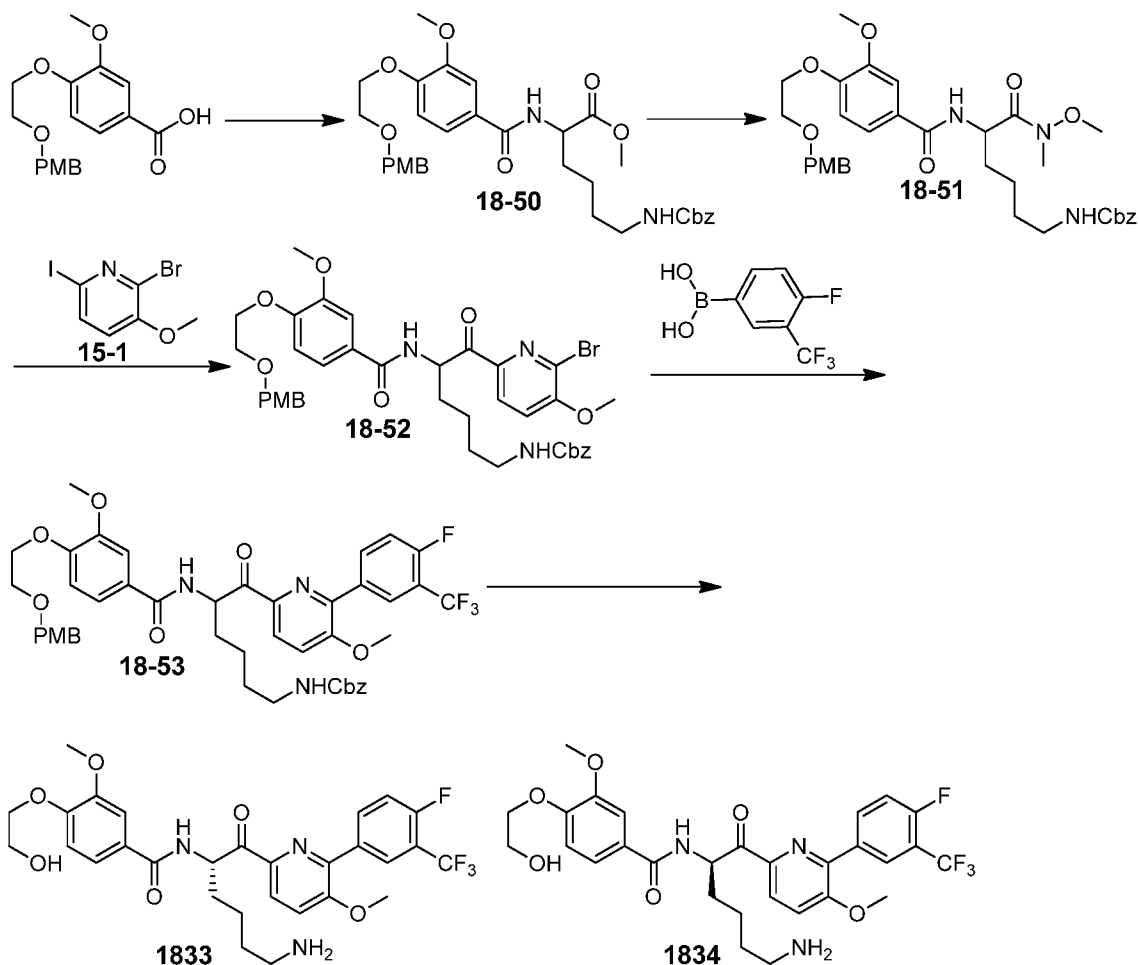
[1041] A 2M *i*-PrMgCl solution in THF (1.58 mL, 3.17 mmol) was added dropwise to a solution of **15-1** (599 mg, 1.91 mmol) and **18-48** (735 mg, 1.27 mmol) in dry THF (15 mL). The mixture was stirred at rt for 1 h and then quenched with MeOH and water. The volatiles were removed under reduced pressure. The aqueous portion was extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 80:20 to 50:50) afforded **18-49** as a pale yellow solid (437 mg, 49%). UPLC/MS(ES⁺), m/z: 703.21 [M+H]⁺.

[1042] A mixture of **18-49** (0.600 mmol), -(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (1.51 mmol), Pd(dppf)Cl₂ (0.042 mmol) and aq Na₂CO₃ (2M solution, 1.50 mmol) in DME (5 mL) was degassed and heated to 85°C. The reaction was monitored by TLC and UPLC. The mixture was diluted with water and extracted three times with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered, concentrated under reduced pressure, and chromatographed. The compound was dissolved in a 10:1 DCM-TFA solution. The mixture was stirred at rt until disappearing of the starting material. The mixture was diluted with DCM and the organic portion was washed with 1M aq NaOH solution and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The mixture of compounds (29 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column (25 x 2.0 cm, 5 uM), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 75/25% v/v, flow rate: 14 mL/min, UV detection DAD 220 nm] to obtain compound **1829** (8.0 mg, enantiomer 1 (*R*), t_R 14.5 min) and compound **1830** (11.9 mg, enantiomer 2 (*S*), t_R 16.4 min) based on the order of elution. UPLC and ¹H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES⁺), m/z: 541.19 [M+H]⁺.



[1043] Compounds **1831** and **1832** (40 mg, 14% over two steps) were prepared starting from **18-49** and (3-chloro-4-fluorophenyl)boronic acid by following a synthetic route, which closely follows that described for preparation of compounds **1829** and **1830**. Compound **1831** (22.2 mg, enantiomer 1 (*R*), t_R 14.4 min) and compound **1832** (14.9 mg, enantiomer 2 (*S*), t_R 16.7 min) based on the order of elution. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES^+), m/z : found 519.25 $[M+H]^+$.

EXAMPLE 18-13
Preparation of Compounds 1833 and 1834



[1044] A mixture of acid **16-3** (750 mg, 2.25 mmol), HOBT (548 mg, 4.06 mmol), EDC (603 mg, 3.15 mmol), TEA (565 μ L, 4.06 mmol) and methyl 2-amino-6-[(benzyloxy)carbonyl]amino}hexanoate (990 mg, 3.37 mmol) in DCM (18 mL) was stirred at room temp for 3 h. A 1M HCl solution was added and the mixture was stirred at room temp for 10 mins. The mixture was filtered from the solids and the layers were separated. The organic portion was washed with 1M aq HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 60:40 to 30:70) afforded **18-50** (2.10 g). UPLC/MS(ES^+), m/z : 609.40 $[\text{M}+\text{H}]^+$.

[1045] Amide **18-50** (2.10 g) was dissolved in a 2:1:1 THF-MeOH- H_2O mixture (24 mL) and treated with LiOH- H_2O (435 mg, 10.3 mmol). After 30 mins, the volatiles were removed under reduced pressure. The residue was partitioned between DCM and 1M aq HCl solution. The layers were separated and the organic portion was dried (Na_2SO_4), filtered and

concentrated under reduced pressure to afford the acid (1.60 g), which was used in the next step. The acid was dissolved in DCM (20 mL), and HOBT (656 mg, 4.80 mmol), EDC (722 mg, 3.77 mmol), TEA (670 mL, 4.84 mmol) and *N,O*-Dimethylhydroxylamine hydrochloride (394 mg, 4.05 mmol) were added to the solution. The mixture was stirred at rt for 3 h. A 1M aq HCl solution was added and the mixture was stirred at rt for 10 mins. The mixture was filtered from the precipitate and the phases were separated. The organic portion was washed with 1M aq HCl solution, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 60:40 to 0:100) afforded **18-51** (820 mg, 57% over three steps). UPLC/MS(ES⁺), m/z: 638.45 [M+H]⁺.

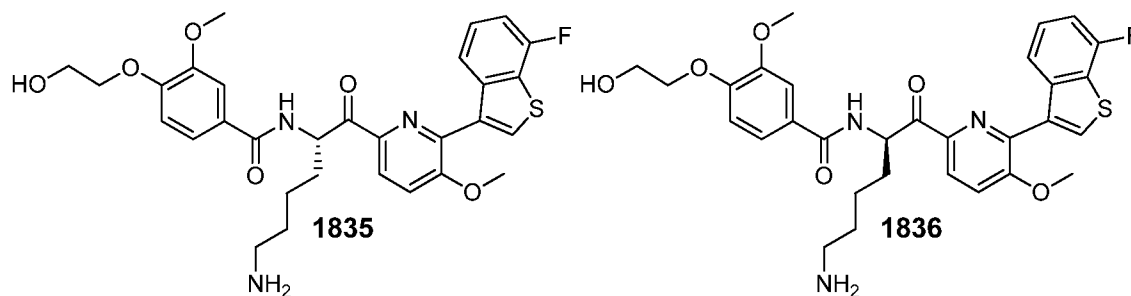
[1046] A 2M *i*-PrMgCl solution in THF (1.60 mL, 3.20 mmol) was added dropwise to a solution of **15-1** (600 mg, 1.92 mmol) and **18-51** (820 mg, 1.28 mmol) in dry THF (16 mL). The mixture was stirred at rt for 30 mins and then quenched with 1M aq HCl solution. The aqueous portion was extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 60:40 to 20:80) afforded **18-52** as an off-white solid (420 mg, 43%). UPLC/MS(ES⁺), m/z: found 764.57 [M+H]⁺.

[1047] Suzuki coupling. A mixture of **18-52** (0.410 mmol), [4-fluoro-3-(trifluoromethyl)phenyl]boronic acid (1.04 mmol), Pd(dppf)Cl₂ (0.020 mmol) and aq Na₂CO₃ (2M solution, 1.04) in DCE (2.5 mL) was degassed and heated to 85°C. The reaction was monitored by TLC and UPLC. The mixture was diluted with water and extracted three times with EtOAc. The combined organic portions were dried (Na₂SO₄), filtered, concentrated under reduced pressure and chromatographed.

[1048] PMB-group removal. A solution of PMB-ether (0.10 mmol) in a 10:1 DCM-TFA mixture (1.1 mL) was stirred at rt until disappearing of the starting material. The mixture was diluted with DCM. The organic portion was washed with 1M aq NaOH solution and brine, dried (Na₂SO₄), filtered, concentrated under reduced pressure and chromatographed.

[1049] Hydrogenation for Cbz-removal. A mixture of Pd/C (10% wet, Degussa type, catalytic) and Cbz-protected amine (0.110 mmol) in EtOH (2 mL) was stirred under H₂ atmosphere (1 atm) for 2 h. The mixture was filtered and concentrated under reduced pressure to afford the crude amine, a mixture of compounds **1833** and **1834**. This mixture of

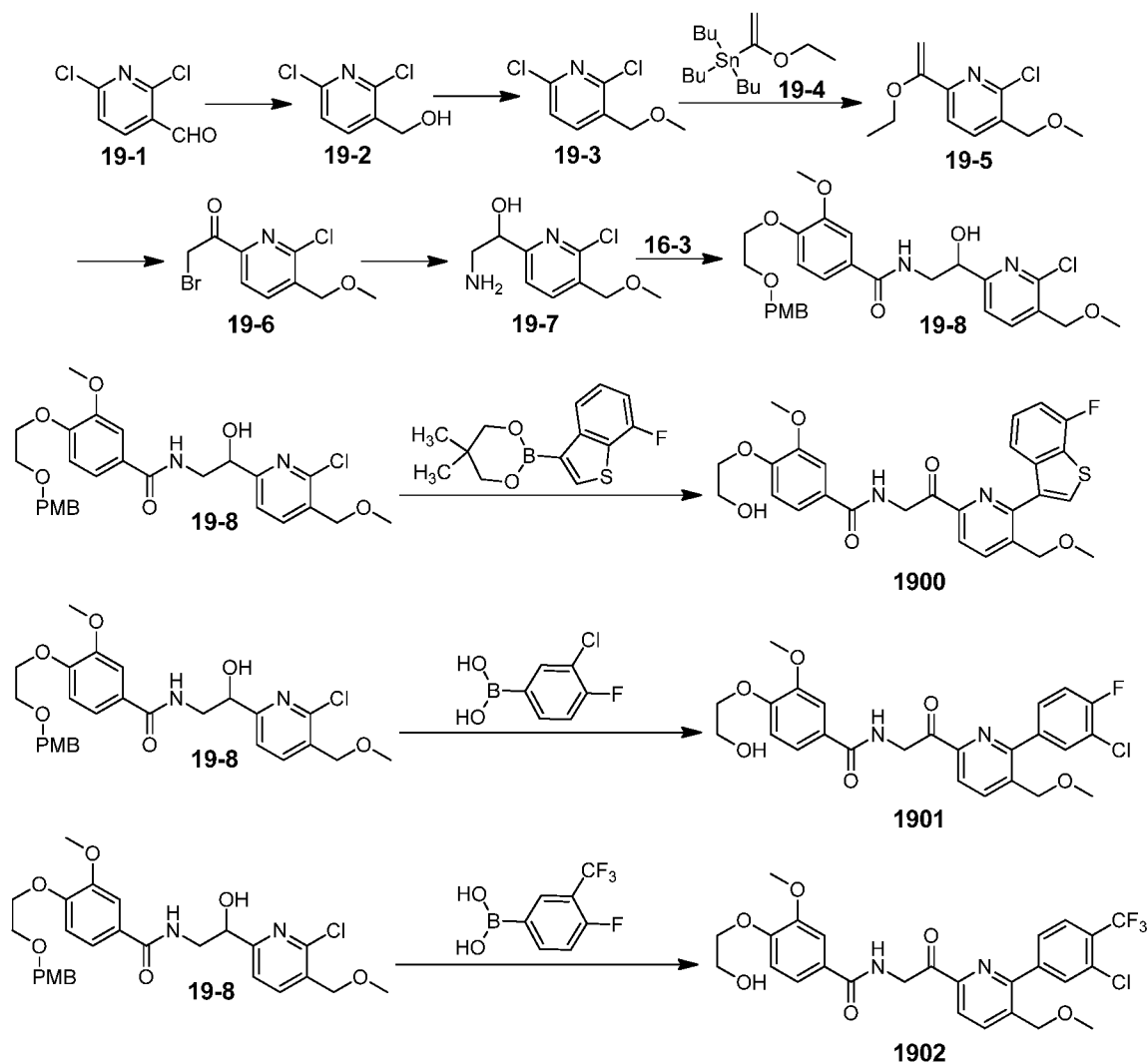
compounds (20 mg) was resolved by using a prep-HPLC separation [Chiralpak IB column (25 x 2.0 cm, 5 μ M), mobile phase: n-Hexane/(Ethanol/Methanol 1/1) 75/25% v/v, flow rate: 15 mL/min, UV detection DAD 220 nm] to obtain compound **1833** (1.5 mg, enantiomer 1, t_R 12.2 min) and compound **1834** (1.0 mg, enantiomer 2, t_R 14.3 min) based on the order of elution. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES^+), m/z: found 594.27 $[\text{M}+\text{H}]^+$.



[1050] Compounds **1835** and **1836** (200 mg) were prepared starting from **18-52** and 2-(7-fluoro-1-benzothiophen-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane by following a synthetic route, which closely follows that described for preparation of compounds **1833** and **1834**.

[1051] Compound **1835** (22 mg, enantiomer 1, t_R 21.0 min) and compound **1836** (17 mg, enantiomer 2, t_R 27.6 min) based on the order of elution separation [Chiralpak IC (25 x 0.46 cm), 5 μ m), mobile phase: n-Hexane / (Ethanol+0.1% isopropylamine) 80/20 % v/v]. UPLC and ^1H NMR analyses for the two enantiomers were superimposable. UPLC/MS(ES^+), m/z: found 582.27 $[\text{M}+\text{H}]^+$.

EXAMPLE 19-1
Preparation of Compounds 1900, 1901 and 1902



[1052] NaBH₄ (476 mg, 12.5 mmol) was added to a solution of **19-1** (2.00 g, 11.4 mmol) in MeOH (25 mL), which had been pre-cooled to 0°C. The mixture was allowed to warm to rt and stirred for 30 mins. A 1M aq HCl solution was added and the organic solvent was removed under reduced pressure. The aqueous phase was extracted three times with DCM. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude **19-2** (2.05 g), which was used in the next step without further purification. UPLC/MS(ES⁺), m/z: 178.00 [M+H]⁺.

[1053] NaH (547 mg, 13.7 mmol) was added to a solution of **19-2** (2.05 g) in dry THF (20 mL), which had been pre-cooled to 0°C. After 20 mins, MeI (1.78 g, 12.5 mmol) was added and the mixture was allowed to warm to rt. After 1 h, the reaction was quenched

with 1M aq HCl solution. The layers were separated and the organic portion was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Crude **19-3** (2.50 g) was used in the next step without further purification.

[1054] A mixture of **19-3** (2.50 g), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (365 mg, 0.52 mmol) and **19-4** (1.77 mL, 5.23 mmol) in 1,4-dioxane (9 mL) was degassed and heated to 90°C . After 1.5 h, the mixture was diluted with EtOAc. The organic portion was washed twice with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford crude **19-5**, which was used in the next step without further purification.

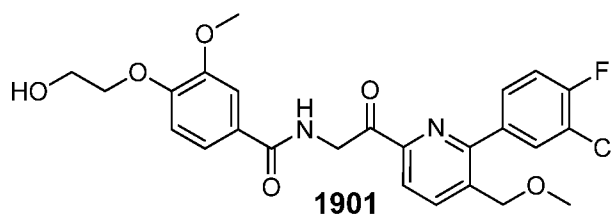
[1055] NBS (1.40 g, 7.84 mmol) was added to a solution of **19-5** in THF (16 mL), which had been pre-cooled to 0°C . The mixture was stirred at 0°C for 45 mins, and then warmed to rt. The reaction was quenched with water, and the layers were separated. The organic portion was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 50:50) afforded **19-6** as a white solid (410 mg, 28% over three steps). UPLC/MS(ES^+), m/z : 277.99 $[\text{M}+\text{H}]^+$

[1056] NaBH_4 (56.0 mg, 1.48 mmol) was added to a solution of **19-6** (410 mg, 1.48 mmol) in MeOH (15 mL). The mixture was stirred at rt for 30 mins. A 1M aq HCl solution was added and the organic solvent was removed under reduced pressure. The aqueous phase was extracted three times with DCM. The combined organic portions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the crude alcohol (396 mg), which was used the next step without further purification. The crude alcohol was dissolved in a 7M NH_3 -MeOH solution (10 mL). The mixture was stirred at rt for 28 h. The volatiles were removed under reduced pressure to give crude **19-7** which was used in the next step without further purification. UPLC/MS(ES^+), m/z : 217.10 $[\text{M}+\text{H}]^+$.

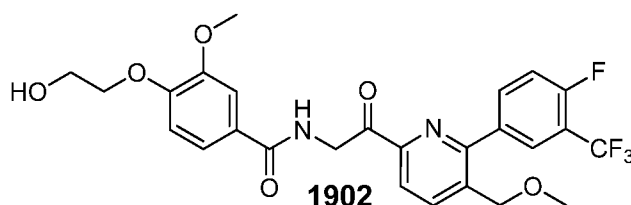
[1057] A mixture of **19-7**, acid **16-3** (637 mg, 1.92 mmol), EDC (426 mg, 2.22 mmol), HOBT (300 mg, 2.22 mmol) and TEA (411 μL , 2.96 mmol) in DCM (7 mL) was stirred at rt for 14 h. The mixture was washed twice with 1M aq HCl solution. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded **19-8** as a white foam (400 mg, 51% over three steps). UPLC/MS(ES^+), m/z : 531.20 $[\text{M}+\text{H}]^+$.

[1058] A mixture of **19-8** (100 mg, 0.188 mmol), the dioxaborinane (124 mg, 0.470 mmol), Pd(dppf)Cl₂ (9.6 mg, 0.013 mmol) and aq Na₂CO₃ (2M solution, 282 uL, 0.564 mmol) in DME (2 mL) was degassed and heated to 85°C. After 2 h, the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 80:20 to 0:100) afforded the protected intermediate (120 mg).

[1059] Dess-Martin periodinane (133 mg, 0.315 mmol) was added to a solution of the protected intermediate (120 mg) in dry DCM (4 mL). The mixture was stirred at rt for 2 h. A 1:1 saturated aq NaHCO₃ solution-saturated aq Na₂S₂O₃ solution was added. The mixture was stirred at rt for 30 mins and the layers were separated. The organic portion was washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude ketone was dissolved in DCM (3 mL) and treated with TFA (200 uL). The mixture was stirred at rt for 1 h. A 2M aq NaOH solution (1 mL) was added and the mixture was stirred at rt for 10 mins. The layers were separated and the aqueous portion was extracted with DCM. The combined organic portions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 80:20) afforded compound **1900** as a white solid (6 mg, 6% over three steps). UPLC/MS(ES⁺), m/z: 525.16 [M+H]⁺.



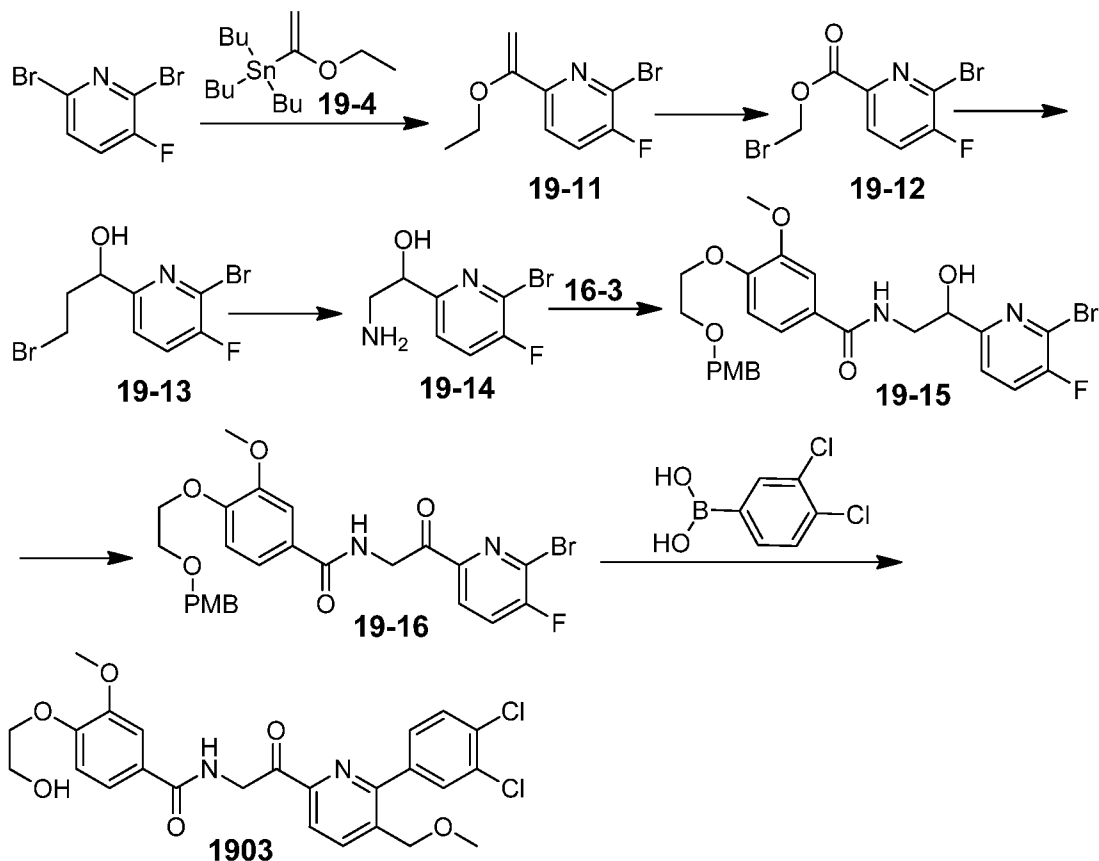
[1060] Compound **1901** was prepared starting from **19-8** and (3-chloro-4-fluorophenyl)boronic acid by following a synthetic route, which closely follows that described for preparation of compound **1900**. Compound **1901** was obtained as an off-white solid (5% over three steps). UPLC/MS(ES⁺), m/z: 503.13 [M+H]⁺.



[1061] Compound **1902** was prepared starting from **19-8** and [4-fluoro-3-(trifluoromethyl)phenyl]boronic acid by following a synthetic route, which closely follows that described for preparation of compound **1900**. Compound **1902** was obtained as an off-white solid (7% over three steps). UPLC/MS(ES⁺), m/z: 537.20 [M+H]⁺.

EXAMPLE 19-2

Preparation of Compound 1903



[1062] A mixture of 2,6-dibromo-3-fluoropyridine (940 mg, 3.68 mmol), Pd(PPh₃)₂Cl₂ (258 mg, 0.368 mmol) and tributyl(1-ethoxyethenyl)stannane (**19-4**, 1.24 mL, 3.68 mmol) in 1,4-dioxane (9 mL) was degassed and heated to 90°C. After 1.5 h, the mixture was diluted with EtOAc. The organic portion was washed twice with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **19-11** was used in the next step without further purification.

[1063] NBS (984 mg, 5.53 mmol) was added to a solution **19-11** in THF (10 mL), which had been pre-cooled to 0°C. The mixture was stirred for 45 min at 0°C, then warmed to reach rt. The reaction was quenched with water and 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 70:30) afforded **19-12** (420 mg, 38% over two steps). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 4.97 (s, 2 H), 8.04 -8.23 (m, 2 H).

[1064] NaBH_4 (59 mg, 1.56 mmol) was added to a solution of **19-12** (420 mg, 1.40 mmol) in MeOH (5 mL). The mixture was stirred at rt for 1 h and then quenched with 1M aq HCl solution. The methanolic portion was removed under reduced pressure and the aqueous phase was extracted three times with DCM. The combined organic portions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford crude **19-13** (380 mg), which was used in the next step. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.66 -3.74 (m, 1 H), 3.76 -3.86 (m, 1 H), 4.88 (q, $J=4.8$ Hz, 1 H), 6.20 (d, $J=5.3$ Hz, 1 H), 7.61 (dd, $J=8.4$, 3.6 Hz, 1 H), 7.90 (t, $J=8.3$ Hz, 1 H).

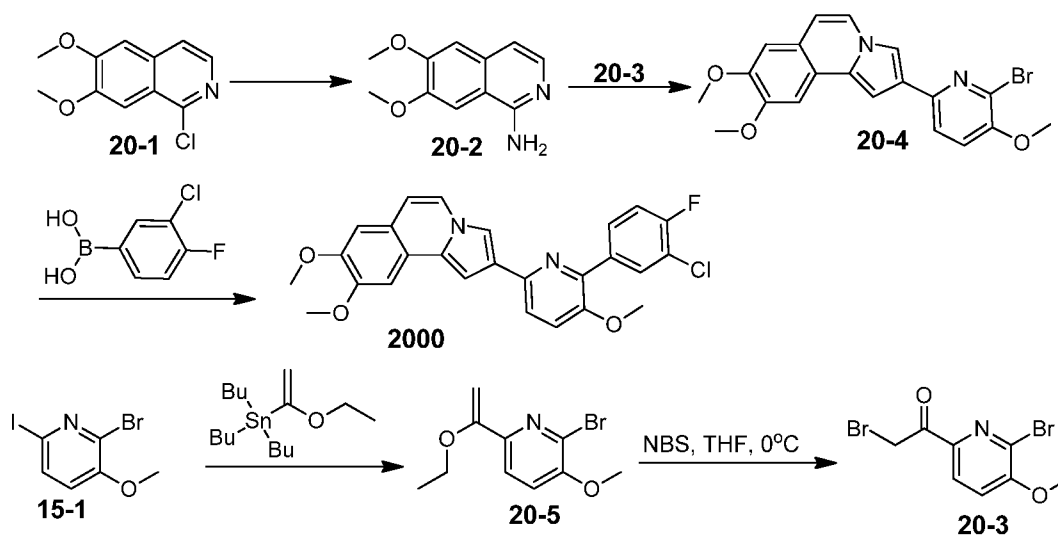
[1065] Bromide **19-13** (380 mg) was dissolved in a 7M NH_3 -MeOH solution (5 mL) and the mixture was stirred at rt for 6 h. The volatiles were removed under reduced pressure to afford **19-14**, which was used in the next step.

[1066] A mixture of **19-14**, 3-methoxy-4-{2-[(4-methoxyphenyl)methoxy]ethoxy}benzoic acid (**16-3**, 548 mg, 1.65 mmol), EDC (364 mg, 1.90 mmol), HOBT (257 mg, 1.90 mmol) and TEA (353 μL , 2.54 mmol) in DCM (10 mL) was stirred at rt for 18 h. The mixture was washed with 1M aq HCl solution. The organic portion was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (DCM-MeOH, 100:0 to 95:5) afforded **19-15** (55.0 mg, 8% over three steps). UPLC/MS(ES^+), m/z : 549.22 $[\text{M}+\text{H}]^+$.

[1067] Dess-Martin periodinane (72 mg, 0.170 mmol) was added to a solution of **19-15** (55 mg, 0.100 mmol) in DCM (4 mL). The mixture was stirred at rt for 1 h and additional DMP (13.0 mg, 0.030 mmol) was added. After 30 mins, a 1:1 saturated aq NaHCO_3 solution-saturated aq $\text{Na}_2\text{S}_2\text{O}_3$ solution was added. The mixture was stirred at rt for 40 mins and the layers were separated. The organic portion was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford crude **19-16**, which was used in the next step. UPLC/MS(ES^+), m/z : 547.23 $[\text{M}+\text{H}]^+$.

[1068] A mixture of **19-16**, (3,4-dichlorophenyl)boronic acid (38.0 mg, 0.200 mmol), Pd(dppf)Cl₂ (3.6 mg, 0.050 mmol) and aq Na₂CO₃ (2M solution, 150 uL, 0.300 mmol) in DCE (1.5 mL) was degassed and heated to 85°C. After 2 h, water was added to the mixture and the layers were separated. The organic portion was washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was dissolved in a 10:1 DCM-TFA solution (4 mL) and the solution was stirred at rt for 20 mins. A 2M aq NaOH solution was added and the layers were separated. The organic portion was dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (EtOAc-MeOH, 100:0 to 90:10) afforded compound **1903** as a light yellow solid (5.0 mg, 10% over three steps). UPLC/MS(ES⁺), m/z: 493.18 [M+H]⁺.

EXAMPLE 20-1
Preparation of Compound 2000



[1069] A mixture of **15-1** (1.00 g, 3.19 mmol), Pd(PPh₃)₂Cl₂ (224 mg, 0.319 mmol) and tributyl(1-ethoxyethenyl)stannane (0.97 mL, 2.87 mmol) in 1,4-dioxane (10 mL) was degassed, heated to 90°C and stirred at that temp for 3 h. The reaction was quenched with saturated aq KF solution and stirred for 10 mins. The organic portion was diluted with EtOAc and washed twice with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude **20-5**, which was used in the next step.

[1070] NBS (738 mg, 4.15 mmol) was added to a solution of **20-5** in THF (20 mL), which had been pre-cooled to 0°C. The mixture was stirred at 0°C for 1 h and then quenched with saturated aq Na₂S₂O₃ solution. The organic portion was washed with brine,

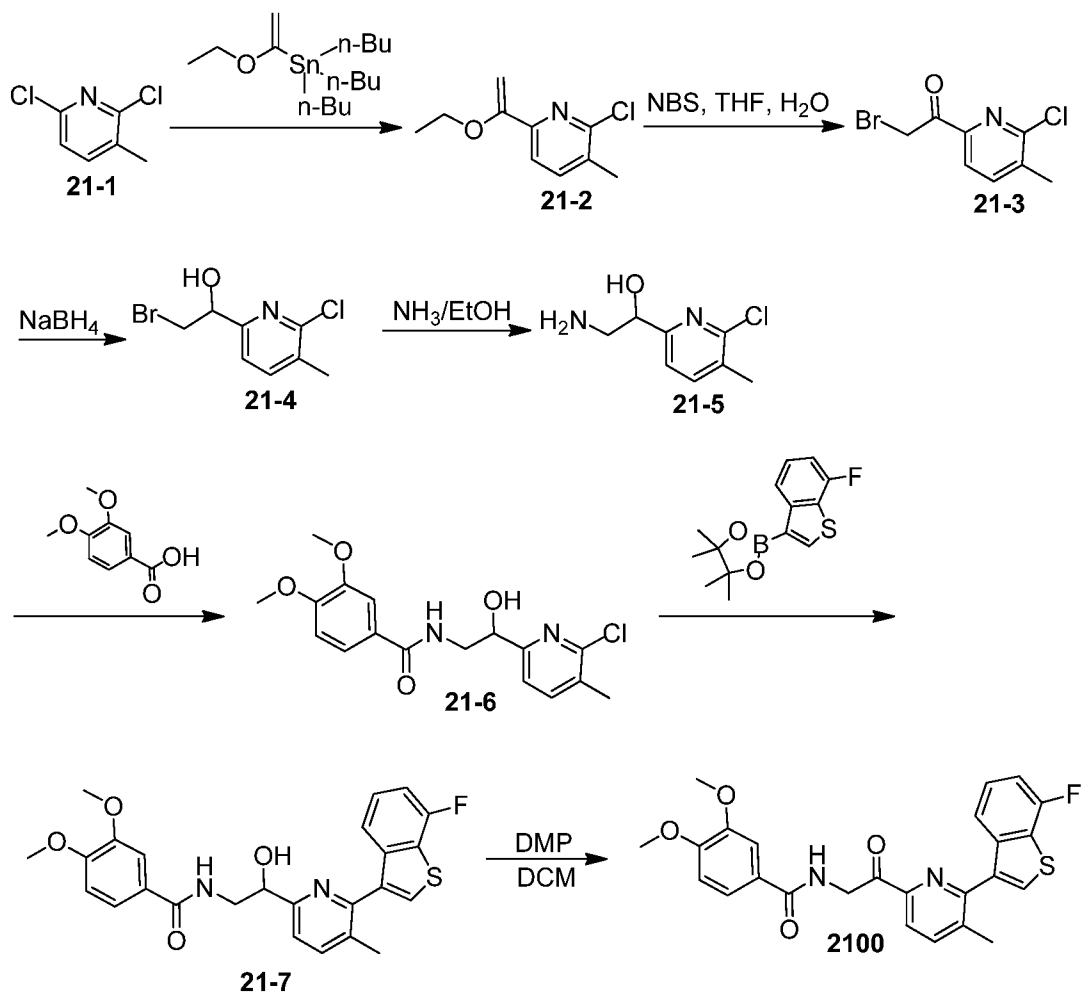
dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 60:40 to 30:70) afforded **20-3** as a white solid. UPLC/MS(ES^+), m/z : 307.96 $[\text{M}+\text{H}]^+$.

[1071] To a mixture of **20-1** (200 mg, 0.890 mmol) and phenol (686 mg, 7.30 mmol) was added powdered KOH (86.5 mg, 1.54 mmol). The mixture was heated to 140°C and stirred at that temp for 3 h. After cooling to rt, the mixture was diluted with 3M aq NaOH solution. The aqueous portion was extracted twice with DCM. The combined organic portions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a phenol-ether, which was used in the next step. This phenol-ether was mixed with ammonium acetate (562 mg, 7.30 mmol). The mixture was heated to 150°C . After 18 h, the mixture was diluted with 3M aq NaOH solution. The aqueous portion was extracted twice with DCM. The combined organic portions were washed with 1M aq HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **20-2** (100 mg), which was used in the next step.

[1072] A mixture of **20-2** (100 mg) and **20-3** (180 mg, 0.588 mmol) in EtOH (3 mL) was heated to reflux. After 18 h, the volatiles were removed under reduced pressure to afford crude **20-4**, which was used in the next step.

[1073] A mixture of **20-4** (50 mg), (3-chloro-4-fluorophenyl)boronic acid (42.1 mg, 0.242 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (2.0 mg, 0.003 mmol) and aq Na_2CO_3 (2M solution, 141 μL , 0.242 mmol) in DCE (2 mL) was degassed and heated to 85°C . After 1 h, the volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 0:100) afforded compound **2000** (A/1454/52/3) as a white solid (18 mg). UPLC/MS(ES^+), m/z : 464.16 $[\text{M}+\text{H}]^+$.

EXAMPLE 21-1
Preparation of Compound 2100



[1074] To a solution of **21-1** (2.5 g, 15.6 mmol), the tin reagent (5.6 g, 15.6 mmol) and KF (1.9 g, 31.7 mmol) in DMF (10 mL) was added Pd(dppf)Cl₂ (330 mg, 0.46 mmol). The system was degassed and then charged with nitrogen three times. The mixture was stirred under nitrogen at 70°C in an oil bath for 10 h. The solution was cooled to rt. The mixture was washed with H₂O and diluted with EA. The EA solution was washed by brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give crude **21-2** (2.3 g), which used in next step without purification. +ESI-MS:m/z 197.9 [M+H]⁺.

[1075] To a solution of **21-2** (2.2 g, 11.2 mmol) in a mixture of THF (10 mL) and H₂O (1 mL) was added NBS (2.1 g, 11.8 mmol), and stirred at rt for 30 mins. The solution was washed with water and the aqueous was extracted by EA. The combined organic layers

were washed by brine, dried over Na₂SO₄ and evaporated to give crude **21-3** (2.0 g), which was used in next step without purification.

[1076] To a solution of **21-3** (2.05 g, 8.1 mmol) in a mixture of THF (10 mL) and MeOH (10 mL) was added NaBH₄ (0.9 g, 23.7 mmol) at -30°C. The mixture was stirred at -30°C for 30 mins. The reaction was quenched by addition of H₂O and extracted by EA. The combined organic layers were washed by brine, dried with Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **21-4** (1.5 g) as an oil. +ESI-MS:m/z 250.0 [M + H]⁺.

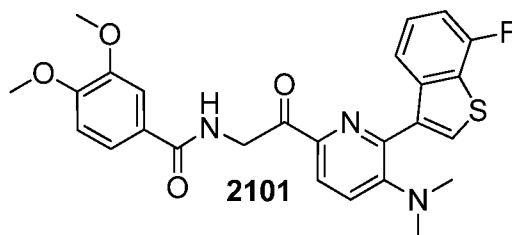
[1077] A mixture of **21-4** (1.5 g, 5.3 mmol) and saturated NH₃/EtOH (10 mL) in a sealed tube was heated to 70°C for 6 h. The solution was removed under reduced pressure to give crude **21-5** (1.0 g), which was used in next step without purification. +ESI-MS:m/z 186.9 [M + H]⁺.

[1078] To a solution of 3,4-dimethoxybenzoic acid (364 mg, 2.0 mmol), HATU (1.1 g, 2.9 mmol) and DIPEA (700 mg, 5.4 mmol) in anhydrous DCM (5 mL) was added **21-5** (372 mg, 2.0 mmol) at 25°C. The solution was stirred for 5 h at this temperature and then diluted with 1.0 N aqueous NaHCO₃ solution. The mixture was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified on a silica gel column (PE:EA=1:1) to give **21-6** (300 mg) as a white solid. +ESI-MS:m/z 351.0 [M + H]⁺.

[1079] To a solution of **21-6** (300 mg, 0.86 mmol) and the dioxaborolane reagent (262 mg, 0.94 mmol) in dioxane (6 mL) were added Pd(PPh₃)₂Cl₂ (30 mg, 0.04 mmol) and a freshly prepared KF solution (200 mg in 1 mL of water). The system was degassed and then charged with nitrogen three times. The mixture was stirred under nitrogen at 70°C in an oil bath for 8 h. The solution was cooled to rt, diluted with EA and separated from the water layer. The EA solution was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column (PE:EA=1:2) to give crude **21-7** (180 mg), which was used in next step without purification.

[1080] To a solution of **21-7** (150 mg, 0.32 mmol) in DCM (5 mL) were added DMP (550 mg, 1.3 mmol). The mixture was stirred at rt for 30 mins with TLC monitoring. The solution was quenched with aq. NaHCO₃ solution and extracted by EA. The combined organic layers were washed with saturated Na₂S₂O₃ and brine, dried over Na₂SO₄ and

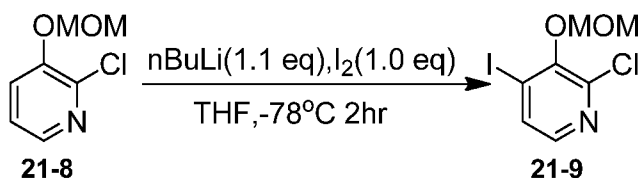
concentrated. The residue was purified by pre-HPLC to give compound **2100** (30 mg) as a white solid. +ESI-MS: m/z 464.9 $[M + H]^+$.



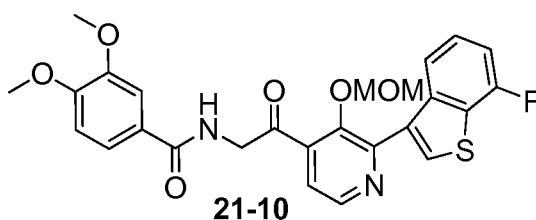
[1081] Compound **2101** was prepared starting from 2,6-dibromo-N,N-dimethylpyridin-3-amine by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2101** was obtained as white solids. +ESI-MS: m/z 493.9 $[M + H]^+$.

EXAMPLE 21-2

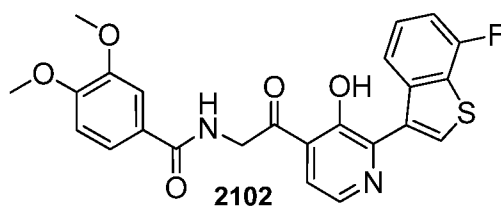
Preparation of Compound 21-9



[1082] Compound **21-8** was prepared according to the procedure in PCT Publication No. WO 2005/074513. Compound **21-9** was prepared according to the procedure in PCT Publication No. WO 2010/018874. PCT Publication Nos. WO 2005/074513 and WO 2010/018874 are incorporated by reference for limited purpose of the preparation of compounds **21-8** and **21-9**, respectively.



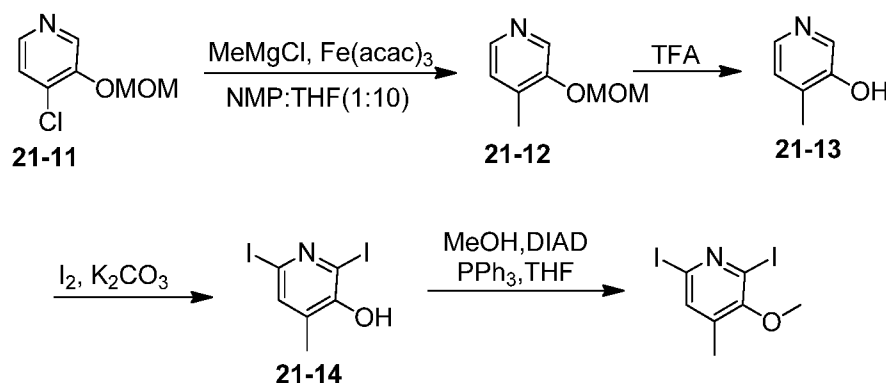
[1083] Compound **21-10** was prepared essentially as described in the preparation of compound **2100** by using **21-9** as the starting material. Compound **21-10** was obtained as white solids. +ESI-MS: m/z 511.0 $[M + H]^+$.



[1084] To a solution of crude **21-10** (30mg, 0.0588 mmol) in DCM (10 mL) was added TFA (7 mL). The mixture was stirred at rt for 30 mins. The mixture was washed with water and extracted with EA. The solution was evaporated at low pressure to give the crude product. The residue was purified by prep-HPLC to generate compound **2102** (4 mg, 8.7 %). +ESI-MS: m/z 467.0 $[M+H]^+$.

EXAMPLE 21-3

Preparation of 2,6-diiodo-3-methoxy-4-methylpyridine



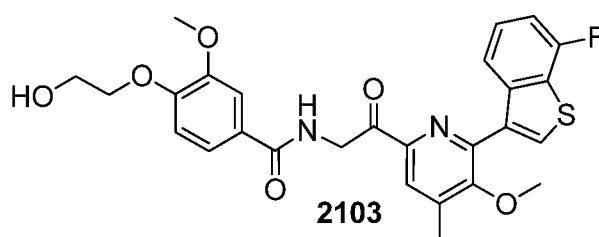
[1085] To a solution of **21-11** (2.1 g, 11.6 mmol) in NMP:THF = 1:10 (10 mL) at 0°C was added Fe(acac)_3 (0.84 g, 23.2 mmol). After 30 mins, MeMgCl (38.6 mL, 116 mmol) was added and the mixture was stirred at rt for 8 h with TLC monitoring. The solution was quenched with MeOH and extracted by EA. The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under low pressure. The residue was purified on a silica gel column (PE:EA=5:1) to give **21-12** (1.2 g, 67.8%) as a liquid.

[1086] The compound **21-13** was prepared essentially as described in the preparation of compound **2102** by using **21-12** as starting material. Compound **21-13** was obtained as white solids. +ESI-MS: m/z 174.0 $[M+H]^+$.

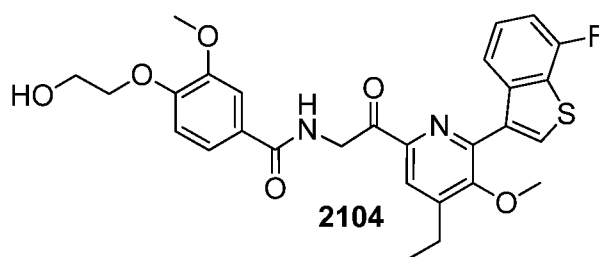
[1087] To a solution of **21-13** (800 mg, 7.3 mmol) and K_2CO_3 (3.0 g, 14.6 mmol) in H_2O (8 mL) / THF (8 mL) was added I_2 (3.7 g, 14.6 mmol) at rt. The mixture was stirred at rt for 30 mins with TLC monitoring. The solution was removed under reduced pressure. The residue was dissolved in EA, and washed with brine. The organic layers were dried over

MgSO₄, and concentrated at low pressure. The residue was purified on a silica gel column (PE:EA=5:1) to give **21-14** (2.2 g, 83.0%). +ESI-MS: m/z 375.9 [M + H]⁺.

[1088] To a solution of **21-14** (2.0 g, 5.5 mmol) and PPh₃ (2.9 g, 11.0 mmol) in THF (800 mL) were added MeOH (1 mL) and DIAD (2.2 g, 11.0 mmol) at rt. The mixture was stirred at 80°C for 2 h with TLC monitoring. The solution was removed under reduced pressure. The residue was purified on a silica gel column (PE:EA=100:1) to give 2,6-diiodo-3-methoxy-4-methylpyridine (1.4 g, 67.3%). ¹H-NMR (400 MHz, CDCl₃), δ=7.44 (s, 1 H), 3.81 (s, 3 H) 2.27 (s, 3 H).



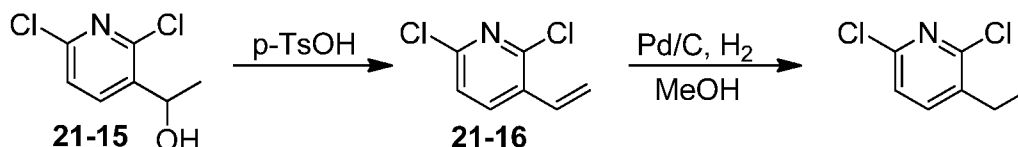
[1089] Compound **2103** was prepared starting from 2,6-diiodo-3-methoxy-4-methylpyridine by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2103** was obtained as white solids. +ESI-MS: m/z 524.9 [M + H]⁺.



[1090] Compound **2104** was prepared starting from pyridine-3-ol by following a synthetic route, which closely follows that described for preparation of compound **2102**. Compound **2104** was obtained as as white solids. +ESI-MS:m/z 539.0 [M + H]⁺.

EXAMPLE 21-4

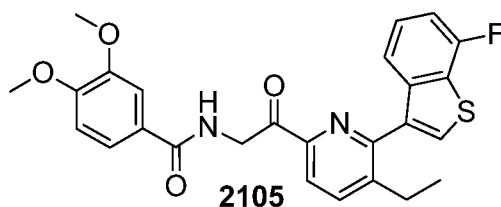
Preparation of 2,6-dichloro-3-ethylpyridine



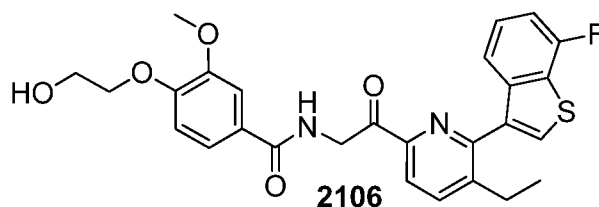
[1091] To a solution of **21-15** (2.0 mg, 11.1 mmol) in chlorobenzene (8 mL) were added p-TsOH (2.1 g, 12.2 mmol) at rt. The mixture was stirred at 140°C in an oil bath for 5

h with TLC monitoring. The reaction was quenched by addition of saturated NaHCO_3 solution and extracted with EA. The EA solution was washed with brine, dried over Na_2SO_4 and concentrated at low pressure. The residue was purified on silica gel column to give **21-16** (0.9 g). $^1\text{H-NMR}$ CDCl_3 (400MHz): δ 7.83 (d, $J=8.0$ Hz, 1 H), 7.27 (m, 1 H), 7.01-6.94 (m, 1 H), 5.79 (d, $J=17.6$ Hz, 1 H), 5.53 (d, $J=11.2$ Hz, 1 H).

[1092] A mixture of **21-16** (2.5 g, 14.4 mmol) in MeOH (10 mL) was added Pd/C (10 %, 300 mg). The system was degassed and then charged with H_2 for 3 times and stirred under H_2 balloon at rt for 1 h. The suspension was filtered through a pad of celite. The combined filtrates were concentrated to give 2,6-dichloro-3-ethylpyridine (2.0 g) as a white solid.



[1093] Compound **2105** was prepared starting from 2,6-dichloro-3-ethylpyridine by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2105** was obtained as white solids. +ESI-MS: m/z 478.9 $[\text{M} + \text{H}]^+$.



[1094] Compound **2106** was prepared starting from 2,6-dichloro-3-ethylpyridine by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2106** was obtained as white solids. +ESI-MS: m/z 508.9 $[\text{M} + \text{H}]^+$.

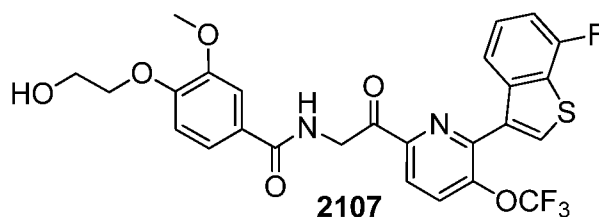
EXAMPLE 21-5

Preparation of 2-bromo-6-iodo-3-(trifluoromethoxy)pyridine

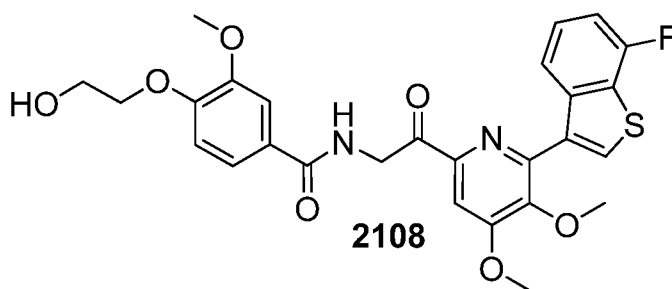


[1095] To a solution of **21-17** (2.0 g, 6.7 mmol) in NMP (10 mL) were added NaH (536 mg, 13.4 mmol) at rt. After 30 mins, CF₂Br₂ (1.68 g, 8.0 mmol) was added, and the mixture was stirred at rt for 1 h with TLC monitoring. The solution was quenched with MeOH and diluted with EA. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated at low pressure. The residue was purified on a silica gel column (PE:EA=10:1) to give **21-18** (1.0 g, 35.1 %).

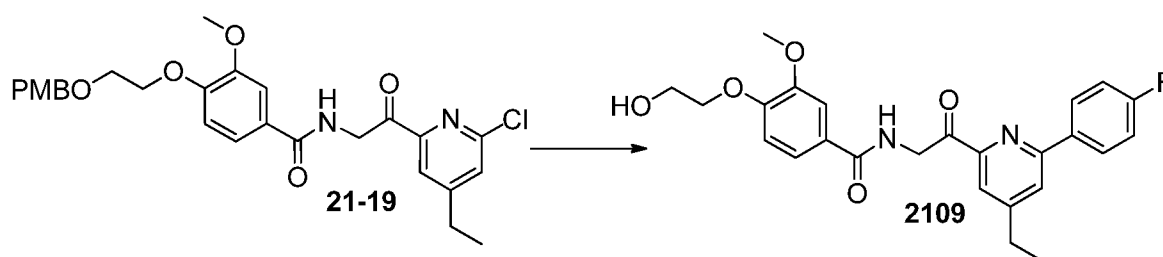
[1096] To a solution of **21-18** (0.8 g, 1.88 mmol) in DCM (10 mL) at -78°C was added AgBF₄ (0.8 g, 4.3 mmol). The mixture was stirred at rt for 8 h with TLC monitoring. The solution was diluted with CH₂Cl₂. The solution were washed by brine, and dried over MgSO₄, and concentrated at low pressure. The residue was purified on a silica gel column (PE:EA=10:1) to give 2-bromo-6-iodo-3-(trifluoromethoxy)pyridine (0.5 g, 72.5 %) as a liquid. +ESI-MS: m/z 367.9 [M + H]⁺.



[1097] Compound **2107** was prepared starting from 2-bromo-6-iodo-3-(trifluoromethoxy)pyridine by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2107** was obtained as white solids. +ESI-MS: m/z 564.9 [M + H]⁺.



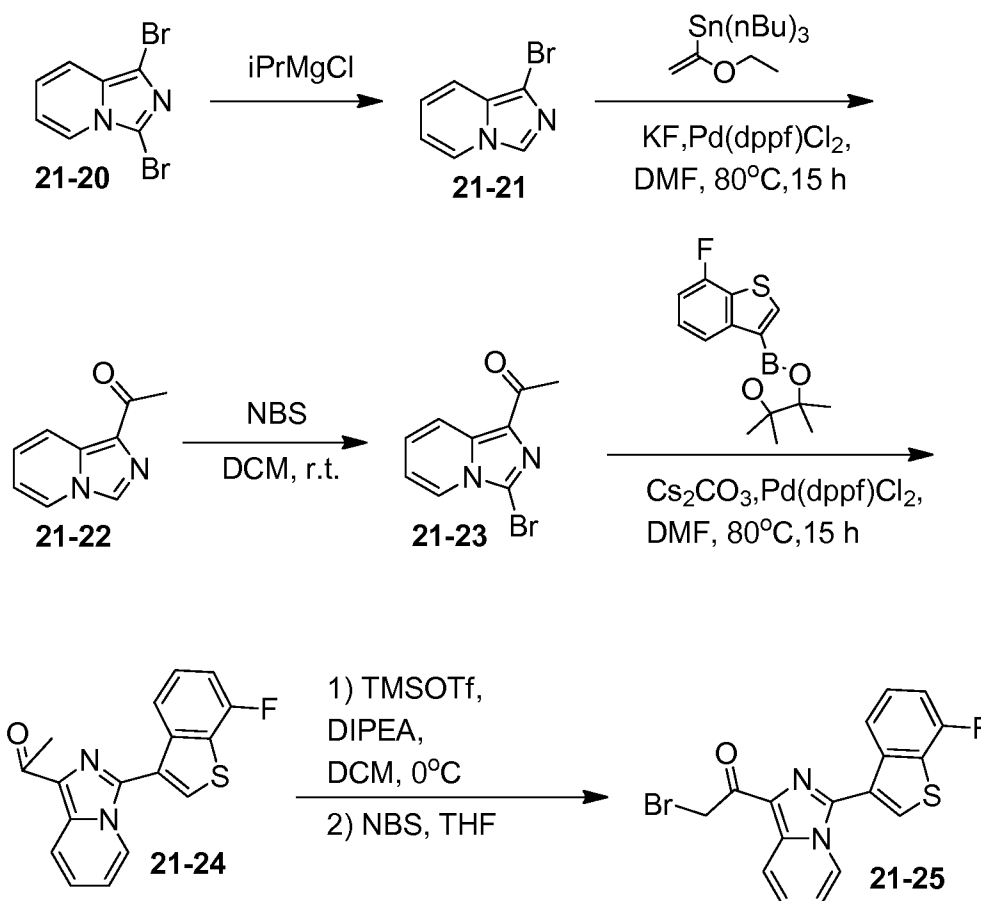
[1098] Compound **2108** was prepared starting from pyridine-3-ol by following a synthetic route, which closely follows that described for preparation of compound **2102**. Compound **2108** was obtained as white solids. +ESI-MS: m/z 541.1 [M + H]⁺.



[1099] Compound **2109** was prepared starting from 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and **21-19** by following a synthetic route, which closely follows that described for preparation of compound **2102**. Compound **2109** was obtained as white solids. +ESI-MS: $m/z = 453.9$ $[M + H]^+$.

EXAMPLE 21-6

Preparation of Compound 21-25



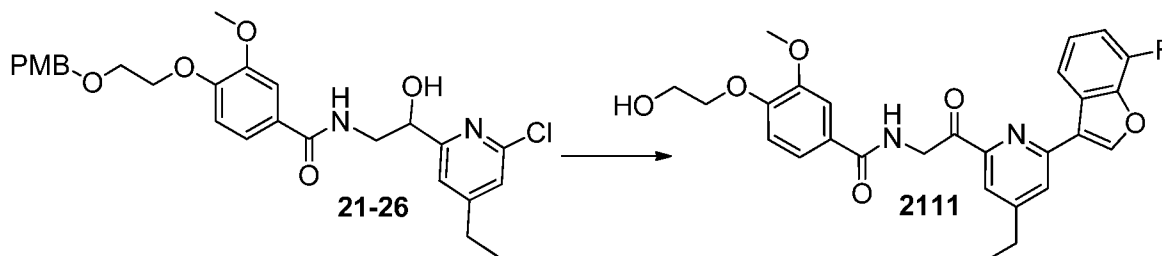
[1100] To a solution of **21-20** (7.5 g, 27.17 mmol) in THF (100 mL) was added slowly *i*-PrMgCl (25 mL, 2M in THF) at rt, and the mixture stirred for 10 mins. The solution was quenched with MeOH and diluted with DCM (20 mL). The solution was washed by brine, dried over Na_2SO_4 and concentrated to give crude **21-21** (5 g, 94.3 %).

[1101] To a solution of **21-21** (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)Cl₂ (372 mg, 0.51 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 rt. The mixture was diluted with EA. The EA solution was washed by brine, dried over Na₂SO₄ and concentrated to give crude **21-22** (360 mg, 44.2%)

[1102] To a solution of **21-22** (360 mg, 2.25 mmol) in DCM (5 mL) was added NBS (480 mg, 2.7 mmol). The mixture was stirred at rt for 30 mins with TLC monitoring. The solution was quenched by aqueous Na₂S₂O₃ solution and extracted by EA. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC(FA) to give **21-23** (250 mg, 46.2%) .

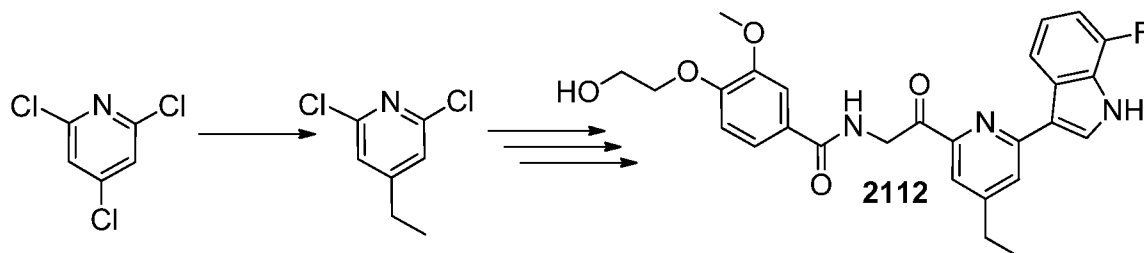
[1103] To a solution of **21-23** (480 mg, 2 mmol) and the dioxaborolane reagent (558 mg, 2 mmol) in dioxane/H₂O (10 mL/2 mL) were added Pd(dppf)Cl₂ (146 mg, 0.2 mmol) and Cs₂CO₃ (975 mg, 3 mmol). The system was degassed and then charged with nitrogen for 3 times. The mixture was stirred under nitrogen at 80°C in an oil bath for 15 h. The solution was cooled to rt, diluted with EA and separated from the water layer. The EA solution was washed by brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **21-24** (400 mg, 64.5%).

[1104] To a solution of **21-24** (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 rt. The solution was concentrated and the residue was dissolved in THF (10 mL) and H₂O (1 mL). NBS (471 mg, 2.65 mmol) was added at rt, 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 **21-25** (600 mg, 86.9%).

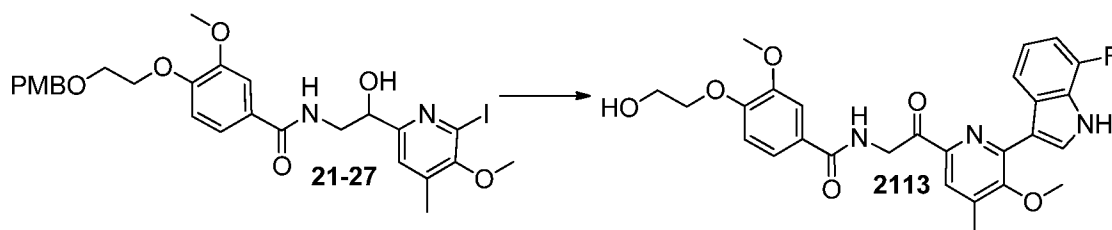


[1105] Compound **2111** was prepared starting from **21-26** and 2-(7-fluorobenzofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane by following a synthetic

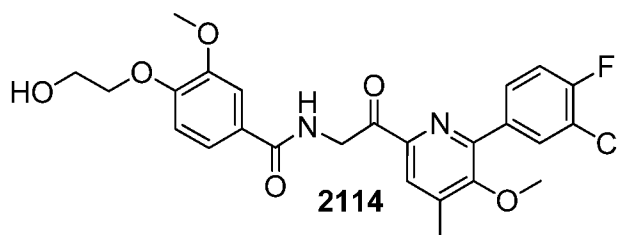
route, which closely follows that described for preparation of compound **2100**. Compound **2111** was obtained as white solids. +ESI-MS: $m/z = 493.0$ $[M + H]^+$.



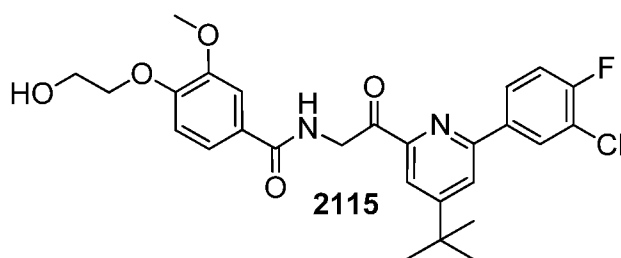
[1106] Compound **2112** was prepared starting from 2,4,6-trichloropyridine by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2112** was obtained as white solids. +ESI-MS: m/z 492.2 $[M + H]^+$.



[1107] Compound **2113** was prepared starting from 7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole and **21-27** by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2113** was obtained as white solids. +ESI-MS: m/z 508.0 $[M + H]^+$.

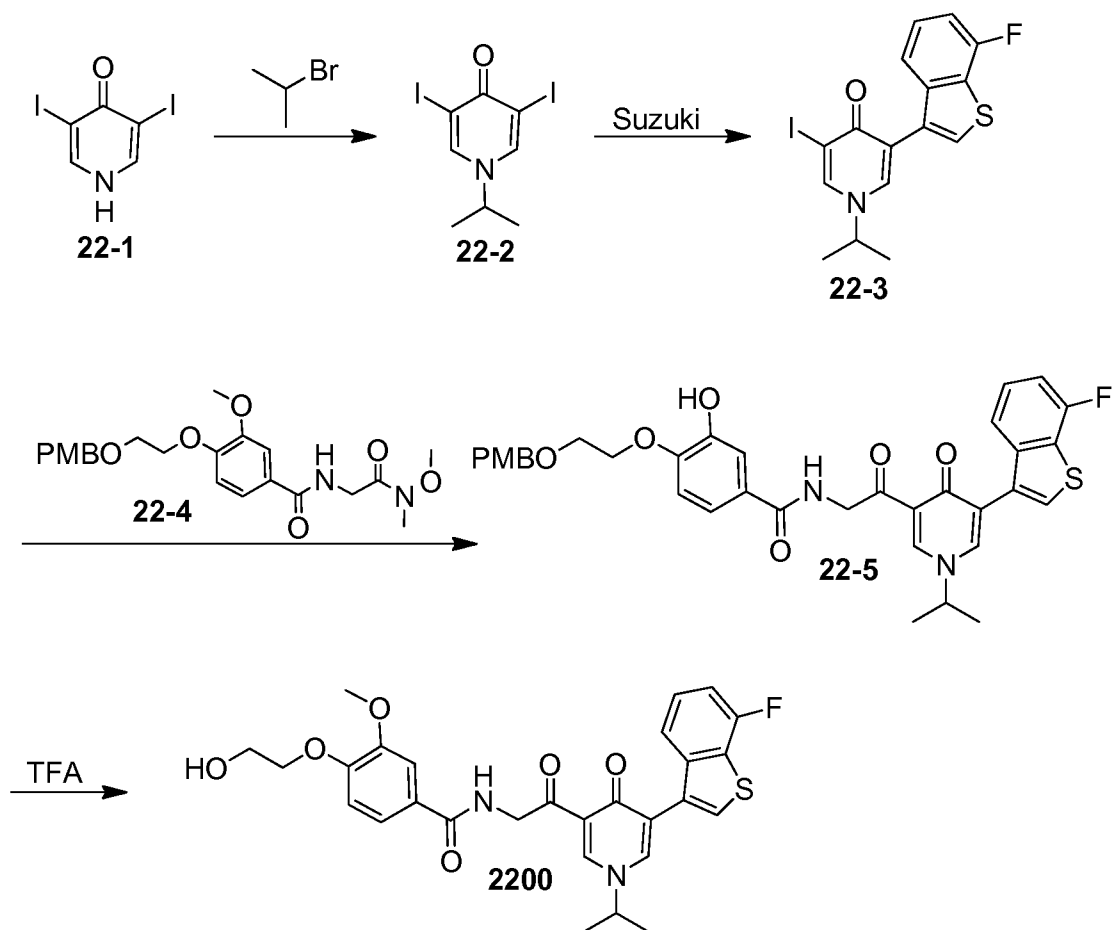


[1108] Compound **2114** was prepared starting from 2-(3-chloro-4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and **21-27** by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2114** was obtained as white solids. +ESI-MS: m/z 502.9 $[M + H]^+$.



[1109] Compound **2115** was prepared starting from (3-chloro-4-fluorophenyl) boronic acid and 2,4,6-trichloropyridine by following a synthetic route, which closely follows that described for preparation of compound **2100**. Compound **2115** was obtained as white solids. +ESI-MS: m/z 514.9 $[M + H]^+$.

EXAMPLE 22-1
Preparation of Compound 2200



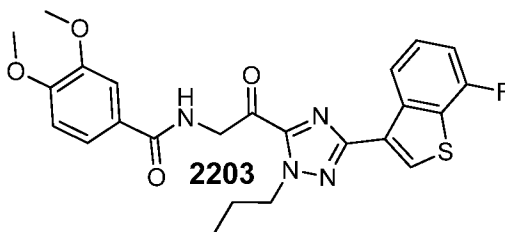
[1110] To a stirred solution of **22-1** (2.4 g, 6.9 mmol) in DMF (10 mL) was added K_2CO_3 (1.98 g, 14 mmol) and *i*-PrBr (1.8 g, 14 mmol), and the mixture was heated to 80°C

for 48 h. The solution was evaporated and purified by column chromatograph gel using PE:EA=3:1 as the elute to give **22-2** (1.0 g, 37.3 %). +ESI-MS: m/z 389.9 $[M+H]^+$.

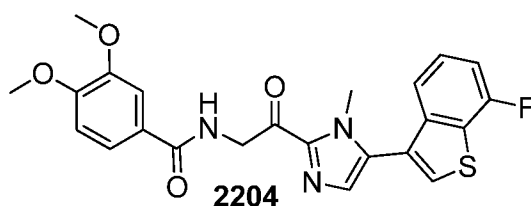
[1111] To a solution of **22-2** (2.5 g, 6.4 mmol) in DME:H₂O=10:1 (10 mL) under N₂ was added Cs₂CO₃ (4.2 g, 12.8 mmol), Pd(dppf)₂Cl₂ (140 mg, 0.2 mmol) and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.95 g, 7 mmol). The mixture was heated to 85°C for 3 h and monitored by TLC (PE:EA=1:3). After conversion, the mixture was filtered and purified by prep-HPLC to give **22-3** (500 mg, 18.9%). ¹H-NMR (400 MHz, CD₃OD), δ =8.52 (d, J =2.21 Hz, 1 H), 8.44 (s, 1 H), 8.10 (d, J =2.21 Hz, 1 H), 7.73 (s, 1 H), 7.31-7.52 (m, 2 H), 7.00-7.19 (m, 1 H), 4.38-4.49 (m, 1 H), 1.51-1.56 (m, 7 H).

[1112] To a solution of **22-3** (300 mg, 0.7 mmol) and **22-4** (289 mg, 0.7 mmol) in THF (10 mL) was added i-PrMgCl (2.2 mL, 2.8 mmol), and stirred at rt for 5 mins. The solution was acidified to pH=8 with aq.NH₄Cl and the aqueous layer was extracted with DCM. The organic layer was combined and concentrated at low pressure. The residue was purified by column chromatograph gel using PE:EA=1:3 as the elute to give **22-5** (80 mg, yield: 17.4 %). +ESI-MS: m/z 645.2 $[M+H]^+$.

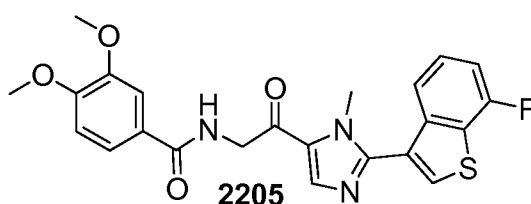
[1113] To a solution of **22-5** (70 mg, 0.11 mmol) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred for 3 h and monitored by TLC, PE:EA=1:3. After conversion, the mixture was concentrated and purified by prep-HPLC to generate compound **2200** (2 mg, 3.5 %). ¹H-NMR (400 MHz, CD₃OD), δ = 8.68 (br. s., 1 H), 8.17 (br. s., 1 H), 7.71-7.98 (m, 1 H), 7.56-7.71 (m, 1 H), 7.53 (br. s., 2 H), 7.47 (br. s., 1 H), 7.40 (br. s., 1 H), 7.01-7.19 (m, 2 H), 4.13 (br. s., 2 H), 3.83 -3.97 (m, 7 H), 1.56 -1.64 (m, 6 H).



[1114] Compound **2203** was prepared using 3,5-dibromo-1H-1,2,4-triazole and by following a synthetic route, which closely follows that described for preparation of compound **1354**. Compound **2203** was obtained as a white solid. +ESI-MS: m/z 483.0 $[M+H]^+$.

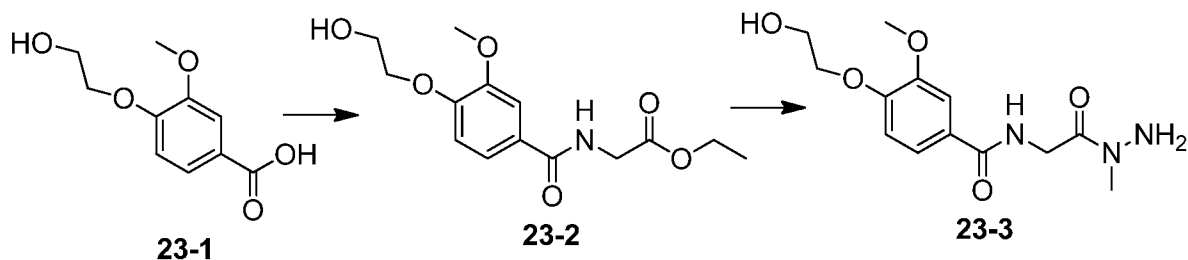


[1115] Compound **2204** was prepared using 2,4,5-tribromo-1*H*-imidazole and by following a synthetic route, which closely follows that described for preparation of compound **1354**. Compound **2204** was obtained as a white solid. +ESI-MS: m/z 454.0 $[M + H]^+$.



[1116] Compound **2205** was prepared using 2,4,5-tribromo-1*H*-imidazole and by following a synthetic route, which closely follows that described for preparation of compound **1355**. Compound **2205** was obtained as a white solid. +ESI-MS: m/z 454.0 $[M + H]^+$.

EXAMPLE 23-1 **Preparation of Compound 23-3**

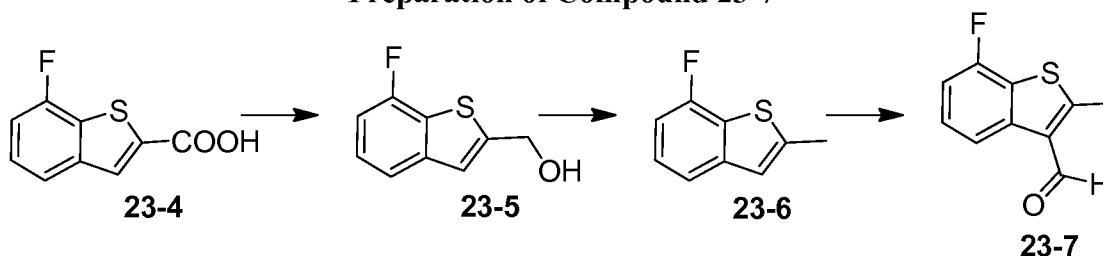


[1117] To a solution of **23-1** (6.0 g, 28 mmol), HATU (15 g, 39 mmol) and DIPEA (9 g, 70 mmol) in anhydrous DCM (100 mL) was added ethyl 2-aminoacetate (3.9 g, 28 mmol) at 25°C. The solution was stirred for 10 h at this temperature. The solution was then diluted with 1.0 N aqueous NaHCO_3 solution, and extracted with EA. The combined organic phase was dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by chromatograph to give **23-2** (4.0 g, 45 %). $^1\text{H-NMR}$ DMSO (400MHz), δ = 8.78-8.75 (br, 1 H), 7.45 (m, 1 H), 7.43 (s, 1 H), 7.01 (d, $J=8.4$ Hz, 1 H),

4.87-4.84 (m, 1 H), 4.11-4.06 (m, 2 H), 4.02-3.95 (m, 4 H), 3.78 (s, 3 H), 3.72-3.69 (m, 2 H), 1.19-1.15 (m, 3 H).

[1118] To a solution of **23-2** (2.5 g, 8.4 mmol) in anhydrous EtOH (15 mL) was added methyl-hydrazine (18.3 g, 39 mmol). The solution was stirred for 10 h at 70°C and then cooled to rt. The solution was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **23-3** (300 mg). ¹H-NMR DMSO (400MHz): δ = 8.26 (br, 1 H), 7.47 (m, 1 H), 7.45 (s, 1 H), 7.02 (d, J=8.4 Hz, 1 H), 4.23 (m, 2 H), 4.04-4.01 (m, 2 H), 3.80 (s, 3 H), 3.74-3.72 (m, 2 H), 3.12 (d, J=3.6 Hz, 3 H).

EXAMPLE 23-2 Preparation of Compound 23-7

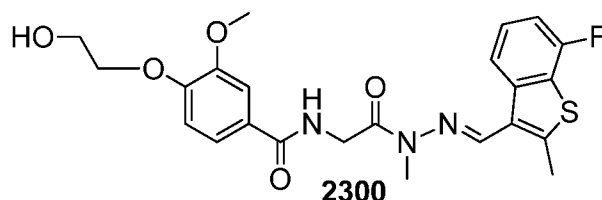


[1119] To a solution of **23-4** (3.0 g, 15.3 mmol) in anhydrous THF (8 mL) was added BH₃/THF (18 mmol) under an argon atmosphere. The solution was stirred at 50°C for 6 h and cooled to rt. The reaction was quenched by addition of MeOH. The mixture was concentrated. The residue was purified on a silica gel column to give **23-5** (2.1 g) as a white solid. ¹H-NMR CDCl₃ (400MHz): δ = 7.62 (d, J= 8.0 Hz, 1 H), 7.39-7.34 (m, 2 H), 7.18-7.13 (m, 1 H), 4.77 (d, J= 0.40 Hz, 1 H).

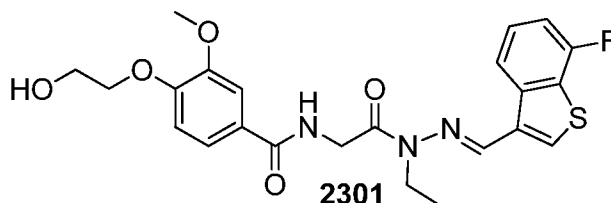
[1120] To a solution of **23-5** (2.1 g, 11.5 mmol) and triethylsilane (2.5 g, 21.5 mmol) in anhydrous EtOH (6 mL) was added a catalytic amount of palladium chloride (10 mol %) under an argon atmosphere. The solution was stirred at rt for 1 h. The mixture was filtered over a pad of celite and the filtrate was concentrated in vacuo. The residue was chromatographed on a silica gel column to give **23-6** (1.66 g) as a white solid. ¹H NMR: CDCl₃ (400MHz): δ = 7.44 (d, J=7.6 Hz, 1 H), 7.29-7.24 (m, 1 H), 7.01-6.93 (m, 2 H), 2.61 (s, 3 H).

[1121] Compound **23-6** (1.66 g, 10 mmol) and dichloro(methoxy) methane (1.60 g, 14.1 mmol) were dissolved in anhydrous DCM (20 mL). Titanium tetrachloride (2.7 g, 14.4 mmol) was added. After 1 h at rt, the mixture was poured into a mixture of saturated

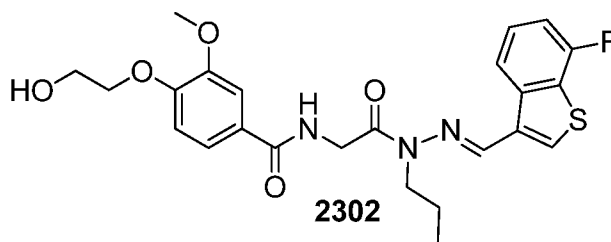
aqueous NaHCO_3 and ice. The mixture was stirred for about 30 mins and then extracted with DCM. The organic layer was dried and concentrated. The residue was purified by chromatograph (PE:EA=60:1 to 10:1) to give **23-7**. (1.5 g, 70 %). $^1\text{H-NMR}$ CDCl_3 (400MHz): δ = 10.35 (s, 1 H), 8.35 (d, J =8.4 Hz, 1 H), 7.44-7.39 (m, 1 H), 7.10-7.05 (m, 1H), 2.94 (s, 3 H).



[1122] To a solution of **23-3** (297 mg, 1.0 mmol) in anhydrous EtOH (6 mL)/AcOH (0.6 mL) was added **23-7** (195 mg, 1.0 mmol). The solution was stirred at 70°C for 10 h and then cooled to rt. The precipitate was collected by filtration. The solid was washed with EA and EtOH to give compound **2300** (150 mg, 30 %). +ESI-LCMS: m/z = 474.1 $[\text{M} + \text{H}]^+$.

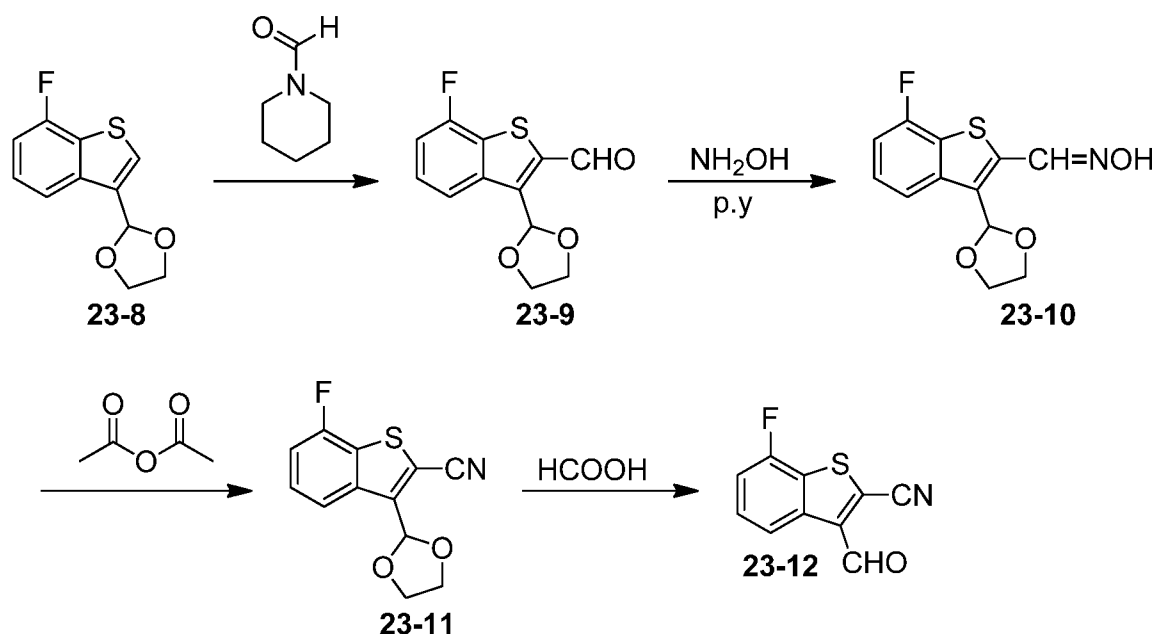


[1123] Compound **2301** was prepared starting from 7-fluorobenzo[b]thiophene-3-carbaldehyde by following a synthetic route, which closely follows that described for preparation of compound **2300**. Compound **2301** was obtained as a white solid. +ESI-MS: m/z 473.9 $[\text{M} + \text{H}]^+$.



[1124] Compound **2302** was prepared starting from 7-fluorobenzo[b]thiophene-3-carbaldehyde by following a synthetic route, which closely follows that described for preparation of compound **2300**. Compound **2302** was obtained as a white solid. +ESI-MS: m/z 488.0 $[\text{M} + \text{H}]^+$.

EXAMPLE 23-3
Preparation of Compound 23-12



[1125] To a solution of **23-8** (224 mg, 1 mmol) in anhydrous THF (10 mL) was added *n*-BuLi (2.5M, 400 μL), and the mixture stirred at -78°C for 15 mins. Piperidine-1-carbaldehyde (226 mg, 2mmol) was added, and the mixture was stirred at -78°C for 30 mins. The mixture was washed with water and extracted with EA. The organic layer was concentrated at low pressure. The residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **23-9** (1.82 mg, 72.2 %) as a white solid.

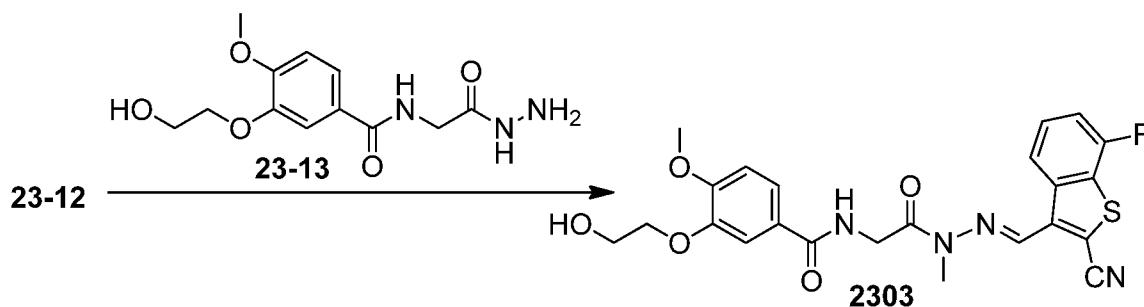
[1126] To a solution of **23-9** (224 mg, 1.0 mmol) in pyridine (10 mL) was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (690 mg, 10.0 mmol). The mixture was stirred at rt overnight. The mixture was diluted with EA, and washed with brine. The organic layer was dried over MgSO_4 , and concentrated at low pressure. The residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **23-10** (1.83 mg, 68.5 %) as a white solid.

[1127] Compound **23-10** (267 mg, 1.0 mmol) was dissolved in acetic anhydride (20 mL), and stirred at 80°C overnight. The mixture was diluted with EA, and washed with saturated NaHCO_3 solution. The organic layer was dried over anhydrous MgSO_4 , and concentrated at low pressure. The residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **23-11** (1.83 mg, 79.5 %) as a white solid. $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz), δ = 7.96 (d, J =8 Hz, 1 H), 7.60-7.61 (m, 2 H), 6.36 (s, 1 H), 4.06-4.13 (m, 4 H).

[1128] Compound **23-11** (249 mg, 1.0 mmol) was dissolved in formic acid (20 mL), and stirred at 80°C overnight. The mixture was diluted with EA, and washed with saturated NaHCO₃ solution. The organic layer was dried over anhydrous MgSO₄, and concentrated at low pressure. The residue was purified by silica gel column (PE/EA = 20/1 to 5/1) to afford **23-12** (1.83 mg, 89.2 %) as a white solid. ¹H-NMR (DMSO-d₆, 400 MHz), δ = 10.4 (s, 1 H), 8.48 (d, *J*=8 Hz, 1 H), 7.51-7.57 (m, 1 H), 7.28 (t, *J* = 8 Hz 1H).

EXAMPLE 23-4

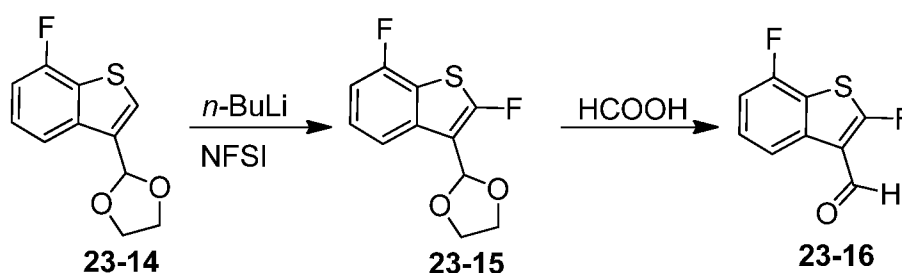
Preparation of Compound 2303



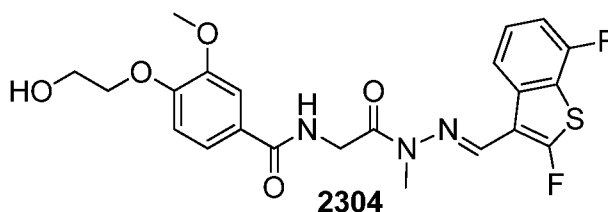
[1129] Compound **2303** was prepared starting from **23-12** and **23-13** by following a synthetic route, which closely follows that described for preparation of compound **2300**. Compound **2303** was obtained as a white solid. +ESI-MS: *m/z* 484.9 [M + H]⁺.

EXAMPLE 23-5

Preparation of Compound 2304

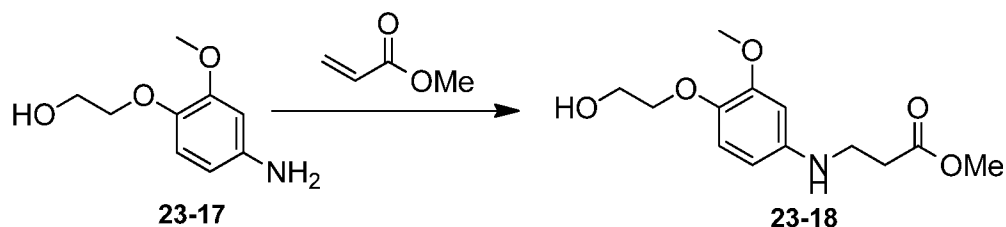


[1130] Compound **23-16** was by following a synthetic route, which closely follows that described for preparation of compound **23-12**.

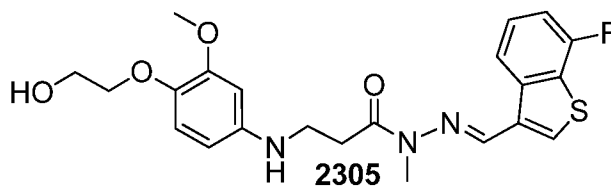


[1131] Compound **2304** was prepared starting from **23-16** and **23-13** by following a synthetic route, which closely follows that described for preparation of compound **2300**. Compound **2304** was obtained as a white solid. +ESI-MS:m/z 478.0 [M + H]⁺.

EXAMPLE 23-6
Preparation of Compound 23-18

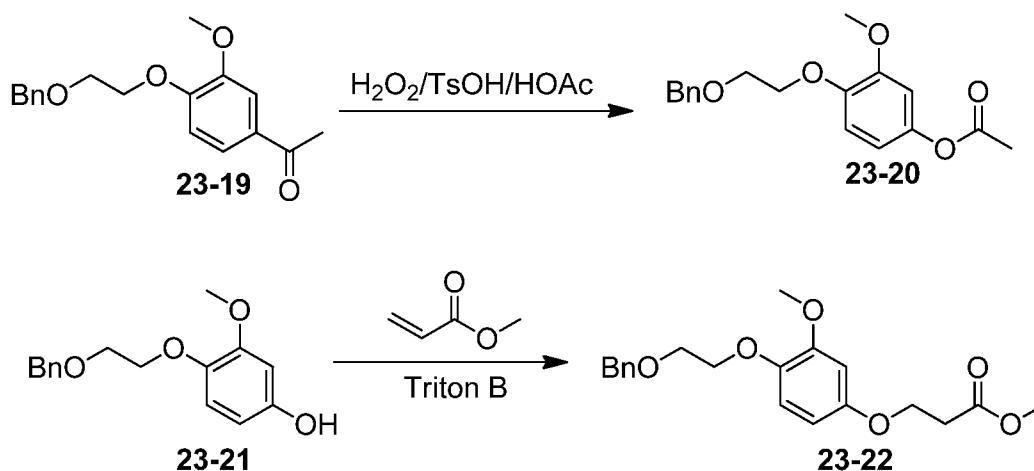


[1132] A solution of crude **23-17** (1.2 g, 6.6 mmol) and methyl acrylate (10 mL) was heated to reflux for 30 h. The solution was evaporated and dissolved with DCM. The solution was acidified to pH=8 with aq.NaHCO₃ and the aqueous layer was extracted with DCM. The organic layer was combined and purified by column chromatograph gel eluted with PE:EA=2:1 to give crude **23-18** (0.40 g, 22.5%).



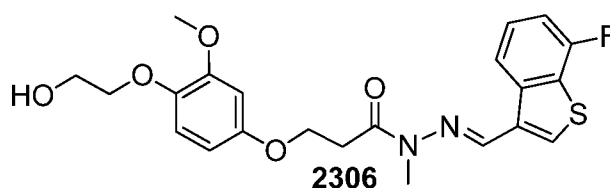
[1133] Compound **2305** was prepared starting from **23-18** and 7-fluorobenzo[b]thiophene-3-carbaldehyde by following a synthetic route, which closely follows that described for preparation of compound **2300**. Compound **2305** was obtained as a white solid. +ESI-MS:m/z 445.9 [M + H]⁺.

EXAMPLE 23-7
Preparation of Compound 23-22



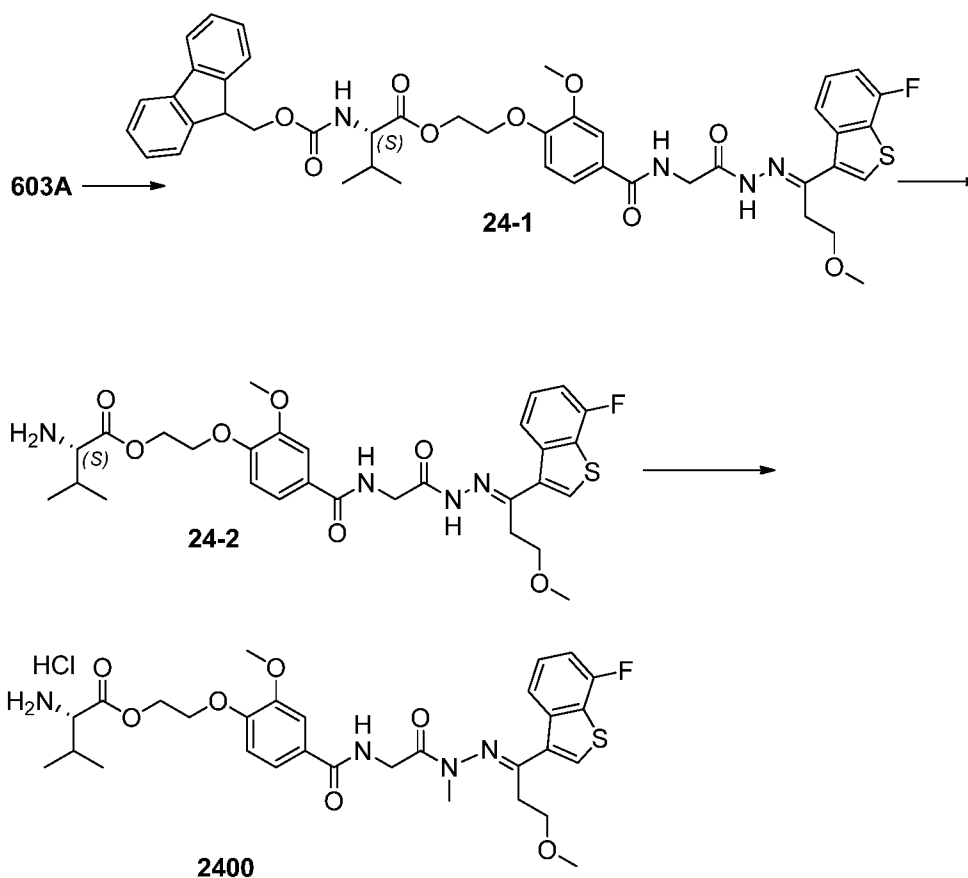
[1134] To a solution of **23-19** (900 mg, 3 mmol), TsOH·H₂O (275 mg, 1.5 mmol) in HOAc (10 mL) at rt was added H₂O₂ (2 mL, 30%). The mixture was heated to 70°C and stirred for 2 h. The solution was poured into water and extracted with EA. The organic phase was dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude **23-20** (800 mg, 84%).

[1135] After converting **23-20** to **23-21**, a solution of **23-21** (548 mg, 2 mmol) and methyl acrylate (5 mL) was combined with Triton B (0.2 mL). The mixture was stirred for 1.5 h at 80°C. The solution was poured into water and extracted with EA. The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude **23-22** (200 mg, 28.0 %).



[1136] Compound **2306** was prepared starting from **23-22** and 7-fluorobenzo[b]thiophene-3-carbaldehyde by following a synthetic route, which closely follows that described for preparation of compound **2300**. Compound **2306** was obtained as a white solid. +ESI-MS: m/z 446.9 [M + H]⁺.

EXAMPLE 24-1
Preparation of Compound 2400

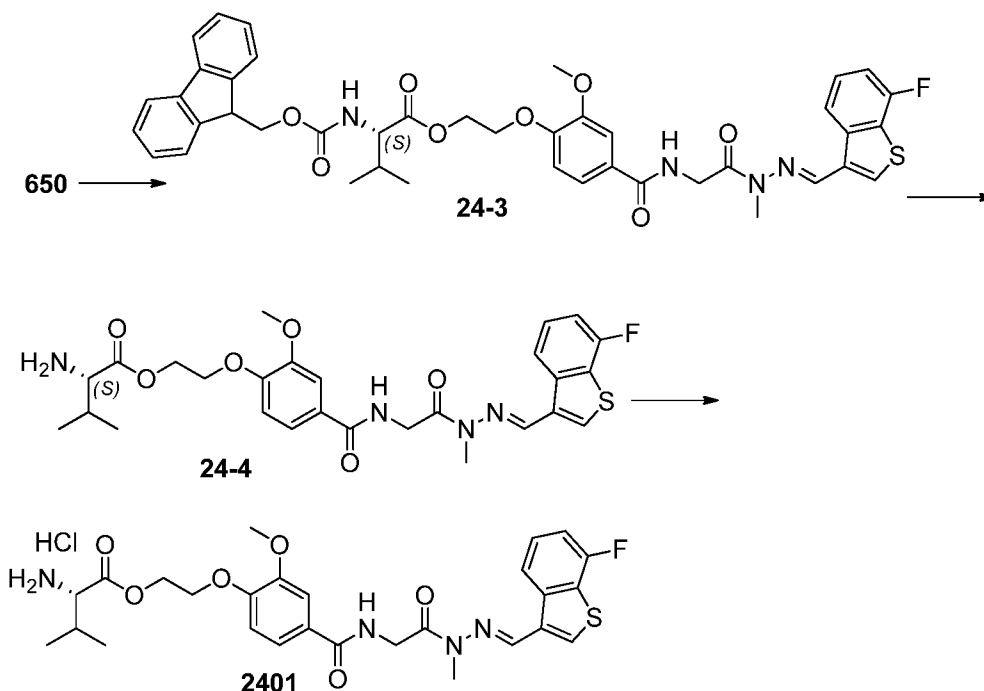


[1137] A mixture of compound **603A** (150 mg, 0.3 mmol), DMAP (15 mg, 0.12 mmol), DCC (186 mg, 0.9 mmol) and Fmoc-Val-OH (305 mg, 0.9 mmol) in THF (3 mL) was stirred at rt for 3 h. The mixture was diluted with EA, washed with water twice, dried over sodium sulfate, and concentrated. Chromatography on silica gel with 20-65% EA in dichloromethane 2 times gave of **24-1** (197 mg) as white foam.

[1138] Compound **24-1** was dissolved in DMF (2 mL) and 10% piperidine in DMF (2 mL) added. The solution stood at rt for 30 mins and was then concentrated to dryness under high vacuum. Chromatography on silica gel with 4-7% methanol in dichloromethane gave pure **24-2** (135 mg) as a white foam. Compound **24-2** (135 mg, 0.224 mmol) was dissolved in MeOH (5 mL) and ammonium chloride (12.0 mg, 0.224 mmol) was added. After standing for 5 mins, the methanol was evaporated on a rotary evaporator, and then the residue was co-evaporated with methanol 4 times. The residue was dissolved water,

filtered, and lyophilized to give compound **2400** (141 mg) as a white foam: +ESI-LCMS: m/z 603.7 $[M + H]^+$.

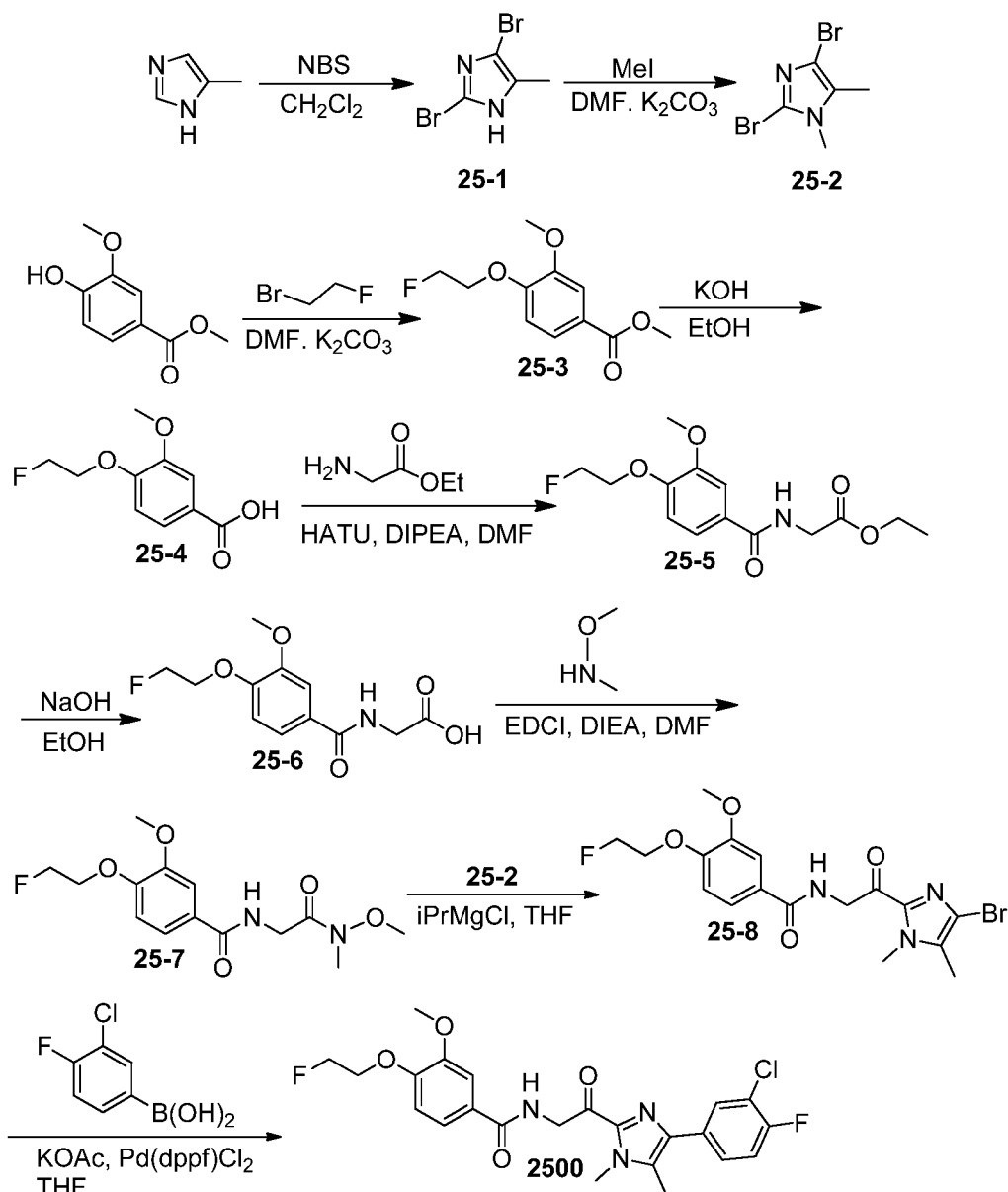
EXAMPLE 24-2
Preparation of Compound 2401



[1139] A mixture of compound **650** (138 mg, 0.3 mmol), DMAP (15 mg, 0.12 mmol), DCC (186 mg, 0.9 mmol) and Fmoc-Val-OH (305 mg, 0.9 mmol) in THF 3 mL) was stirred at rt overnight. DMF (0.8 mL) was added, and the mixture stirred for an additional 3 h. The mixture was diluted with EA, washed with water 4 times, dried over sodium sulfate, and concentrated. Chromatography on silica gel with 1-2% methanol in dichloromethane 2 times gave **24-3** as a white foam, which was dissolved in 5% piperidine in DMF (4 mL). The solution stood at rt for 30 mins and then concentrated to dryness under high vacuum. Chromatography on silica gel with 2-6% MeOH in dichloromethane gave pure **24-4** (143 mg).

[1140] Pure **24-4** (143 mg, 0.256 mmol) was dissolved in MeOH (5 mL) and ammonium chloride (13.7 mg, 0.256 mmol) added. After standing for 5 mins, the methanol was evaporated on a rotary evaporator, and then the residue was co-evaporated with methanol once. The residue was dissolved water, filtered, and lyophilized to give compound **2401** (152 mg) as a white foam. +ESI-LCMS: m/z 559.4 $[M + H]^+$.

EXAMPLE 25-1
Preparation of Compound 2500



[1141] 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 rt. The product was filtered and partitioned between EA and saturated NaHCO_3 . The product was precipitated from MeOH/ CH_2Cl_2 to provide **25-1** (4.31 g, 75 %). ^1H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H).

[1142] To a solution of **25-1** (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 **25-2** (1.6 g, 41%). ^1H NMR (400 MHz, CDCl_3): δ 3.52 (s, 3H), 2.21 (s, 3H).

[1143] 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 **25-3** (8.92 g, 103 %). ^1H 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).

[1144] To a solution of **25-3** (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 **25-4**. (5.0 g, 30 %). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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).

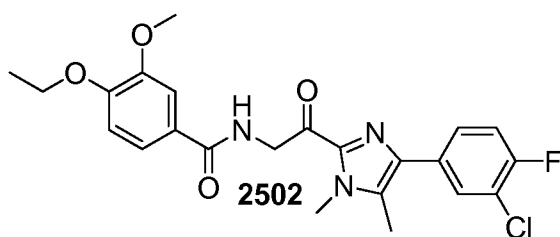
[1145] To a solution of **25-4** (3.07 g, 14.3 mmol), glycine methyl ester HCl salt (3.6 g, 29 mmol), HATU (6.5 g, 17 mmol) in DMF (15 mL) was added DIEA (10 mL, 57 mmol). The solution was stirred for 18 h at rt. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, NaHCO_3 and brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **25-5** (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).

[1146] To a solution of **25-5** (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 rt. The mixture was concentrated, acidified with 2N HCl and extracted with EA to provide **25-6**. (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).

[1147] To a solution of **25-6** (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 rt. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, NaHCO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **25-7** (0.28 g, 47%). ¹H NMR (400 MHz, CDCl₃): 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).

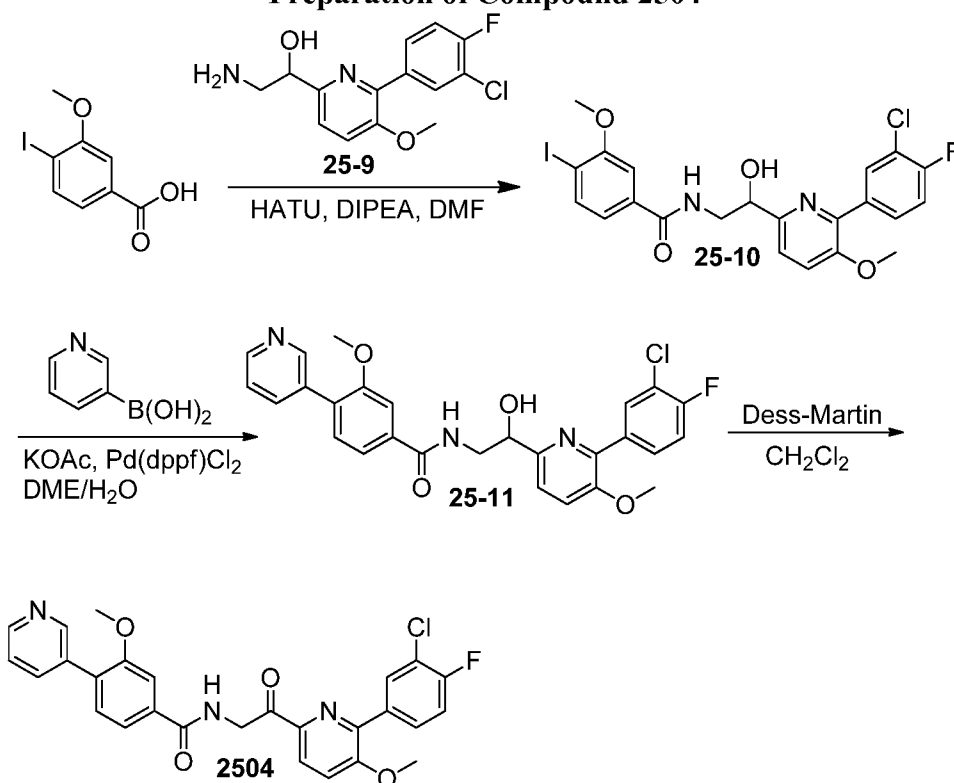
[1148] Isopropylmagnesium chloride (2.0M, 0.48 mL, 0.95 mmol) was added dropwise to a solution of **25-7** (0.12 g, 0.38 mmol) and **25-2** (0.13 g, 0.50 mmol) in THF (1.0 mL). The solution was stirred for 2 h at rt. The reaction was quenched with 1N HCl, diluted with EA and washed with brine. The organic solution was filtered to **25-8** (0.030 g, 20%). ¹H NMR (400 MHz, CDCl₃): 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).

[1149] A solution of **25-8** (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)Cl₂ (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 compound **2500** (24 mg, 72%). LC/MS: [M+H] 478.10.



[1150] Compound **2502** was prepared using iodoethane in the alkylation step and by following a synthetic route, which closely follows that described for preparation of compound **2500**. LC/MS: [M+H] 460.05.

EXAMPLE 25-2
Preparation of Compound 2504

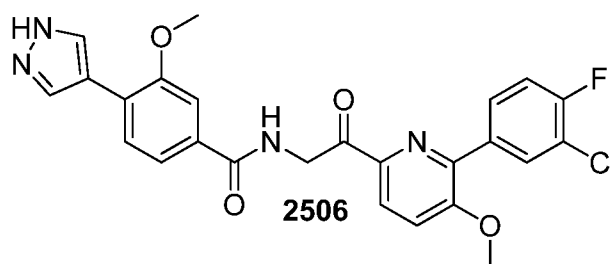


[1151] To a solution of 3-methoxy-4-iodobenzoic acid (0.45 g, 1.6 mmol), **25-9** (0.485 g, 1.6 mmol), HATU (0.75 g, 2.0 mmol) in DMF (3 mL) was added DIEA (0.71 mL, 4.1 mmol). The solution was stirred for 18 h at rt. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, NaHCO_3 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 **25-10** (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).

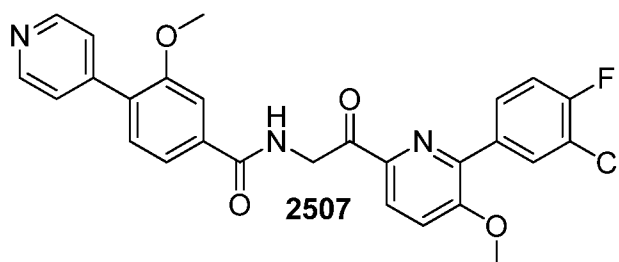
[1152] A solution of **25-10** (25 mg, 0.045 mmol), pyridine-3-boronic acid (11 mg, 0.09 mmol), potassium acetate (13 mg, 0.13 mmol) and Pd(dppf)Cl_2 (6 mg, 0.009 mmol) in DME (0.5 mL) and H_2O (0.05 mL) was heated under microwave irradiation for 1 h at 110°C . The mixture was concentrated and purified by chromatography on silica gel (MeOH/ CH_2Cl_2) to give **25-11** (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, 3H), 3.68-3.75 (m, 1H).

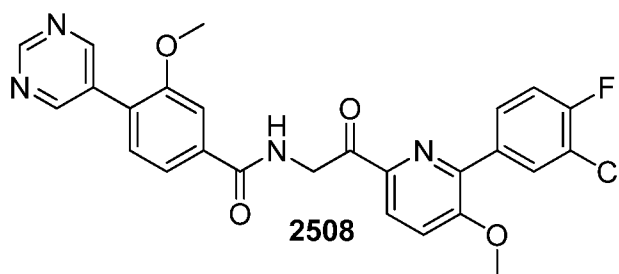
[1153] Dess-Martin periodinane (25 mg, 0.061 mmol) was added to a solution of **25-11** (22 mg, 0.043 mmol) in CH₂Cl₂, and stirred for 2 h. The mixture was diluted with CH₂Cl₂, washed with saturated Na₂CO₃, and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EA/hexane) to give compound **2504** (6.1 mg, 28%). LC/MS: [M+H] 506.10.



[1154] Compound **2506** was prepared using pyrazole-4-boronic acid pinacol ester in the Suzuki reaction and by following a synthetic route, which closely follows that described for preparation of compound **2504**. LC/MS: [M+H] 495.10.

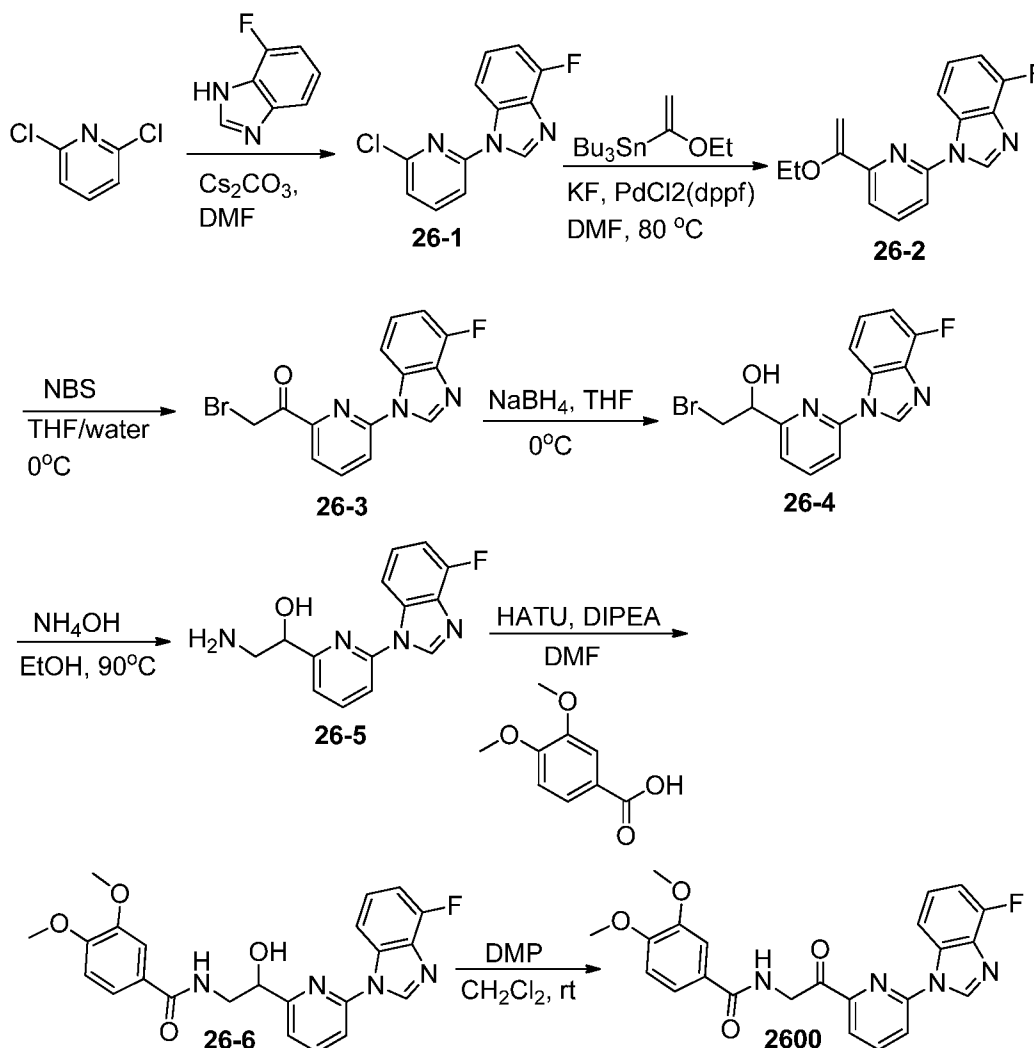


[1155] Compound **2507** was prepared using pyridine-4-boronic acid pinacol ester in the Suzuki reaction and by following a synthetic route, which closely follows that described for preparation of compound **2504**. LC/MS: [M+H] 506.10.



[1156] Compound **2508** was prepared using pyrimidine-4-boronic acid pinacol ester in the Suzuki reaction and by following a synthetic route, which closely follows that described for preparation of compound **2504**. LC/MS: [M+H] 507.10.

EXAMPLE 26-1
Preparation of Compound 2600



[1157] 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 rt. The mixture was diluted with EtOAc and washed with a saturated 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 **26-1** (300 mg) as a white solid. LCMS: 248.1 m/z $[M+H]^+$.

[1158] To a stirring mixture of **26-1** (300 mg, 1.056 mmol), KF (184 mg, 3.2 mmol), Pd(dppf)Cl₂ (155 mg, 0.2 mmol) in dry DMF (2 mL, deoxygenated prior to use) was added tributyl(1-ethoxyvinyl)stannane (381 mg, 1.056 mmol). The mixture was stirred at 85°C for 1 h. The mixture was cooled to rt and directly loaded into a silica gel column to give **26-2** as a colorless oil. LCMS: 284.2. m/z $[M+H]^+$.

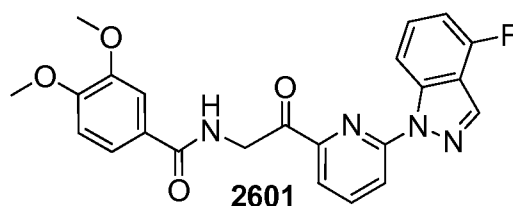
[1159] To a stirred solution of **26-2** (130 mg, 0.46 mmol) in THF/water (1.6 mL/0.8 mL) at 0°C was added NBS (86 mg, 0.48 mmol). The mixture was stirred at 0°C for 15 mins. The mixture was then quenched with a saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **26-3** was used in the next step without any purification.

[1160] To this stirring mixture of **26-3** in MeOH/THF (1:3, 4 mL total volume) at 0°C was added NaBH₄ (17.5 mg). The mixture was stirred for 10 mins at 0°C. The reaction was quenched with a saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **26-4** was used in the next step without any purification.

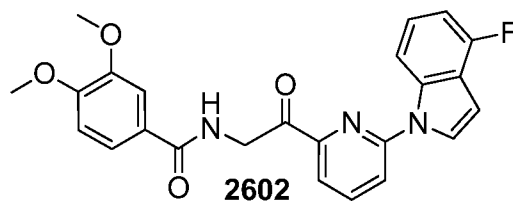
[1161] To a stirring mixture of **26-4** in EtOH (2 mL) was added an ammonia hydrate solution (2 mL) in a sealed tube. The mixture was heated at reflux for 1 h and then cooled to rt. The mixture was diluted with toluene and concentrated under reduced pressure. This process was repeated twice. The mixture was used in the next step without further purification.

[1162] To a stirring mixture of 3,4-dimethoxybenzoic acid (54 mg, 0.3 mmol) in DMF (2 mL) at rt were added HATU (127 mg, 0.33 mmol) and DIPEA (83 mg, 0.64 mmol). The mixture was reacted at rt for 10 mins. To this mixture was added a solution of **26-5** in DMF (1 mL). The mixture was stirred at rt for 1 h and then quenched with a saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue afforded **26-6** (100 mg) as a yellow oil. LC/MS: 437.25 m/z $[M+H]^+$.

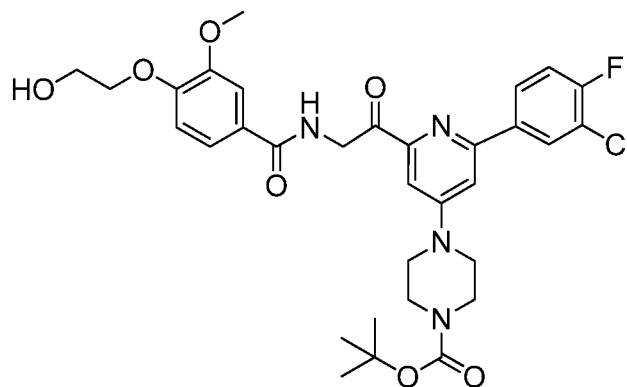
[1163] To a stirring mixture of **26-6** (100 mg, 0.22 mmol) in DCM (2 mL) at rt was added Dess–Martin periodinane (650 mg, 1.53 mmol). The mixture was stirred at rt for 1 h and then slowly quenched with 5% NaHSO₃ and a saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product mixture was purified using prep-HPLC to afford compound **2600** as a white solid. LCMS: 435.25 m/z [M+H]⁺.



[1164] Compound **2601** was prepared using 2,6-dichloropyridine and 7-fluoro-1H-indazole and by following a synthetic route, which closely follows that described for preparation of compound **2600**. LCMS: 435.30 m/z [M+H]⁺.

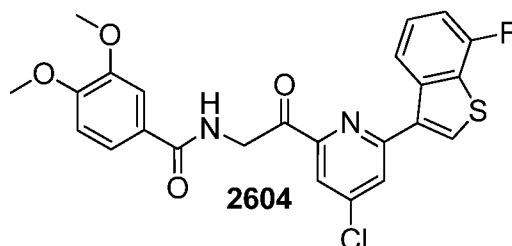


[1165] Compound **2602** was prepared using 2,6-dichloropyridine and 7-fluoro-1H-indole and by following a synthetic route, which closely follows that described for preparation of compound **2600**. LCMS: 434.25 m/z [M+H]⁺.

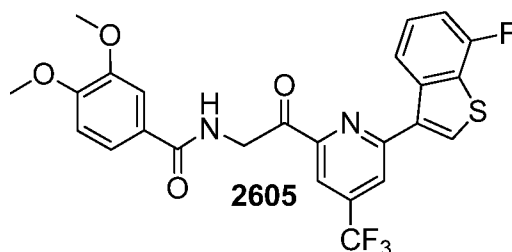


[1166] Compound **2603** was prepared using 1-piperazinecarboxylic acid, 4-(2,6-dichloro-4-pyridinyl)-, 1,1-dimethylethyl ester and by following a synthetic route, which

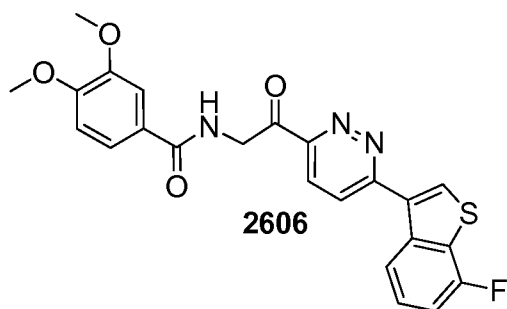
closely follows that described for preparation of compound **2600**. LCMS: 643.20 m/z $[M+H]^+$.



[1167] Compound **2604** was prepared using 2,4,6-trichloropyridine and 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and by following a synthetic route, which closely follows that described for preparation of compound **2600**. LCMS: 485.25 m/z $[M+H]^+$.

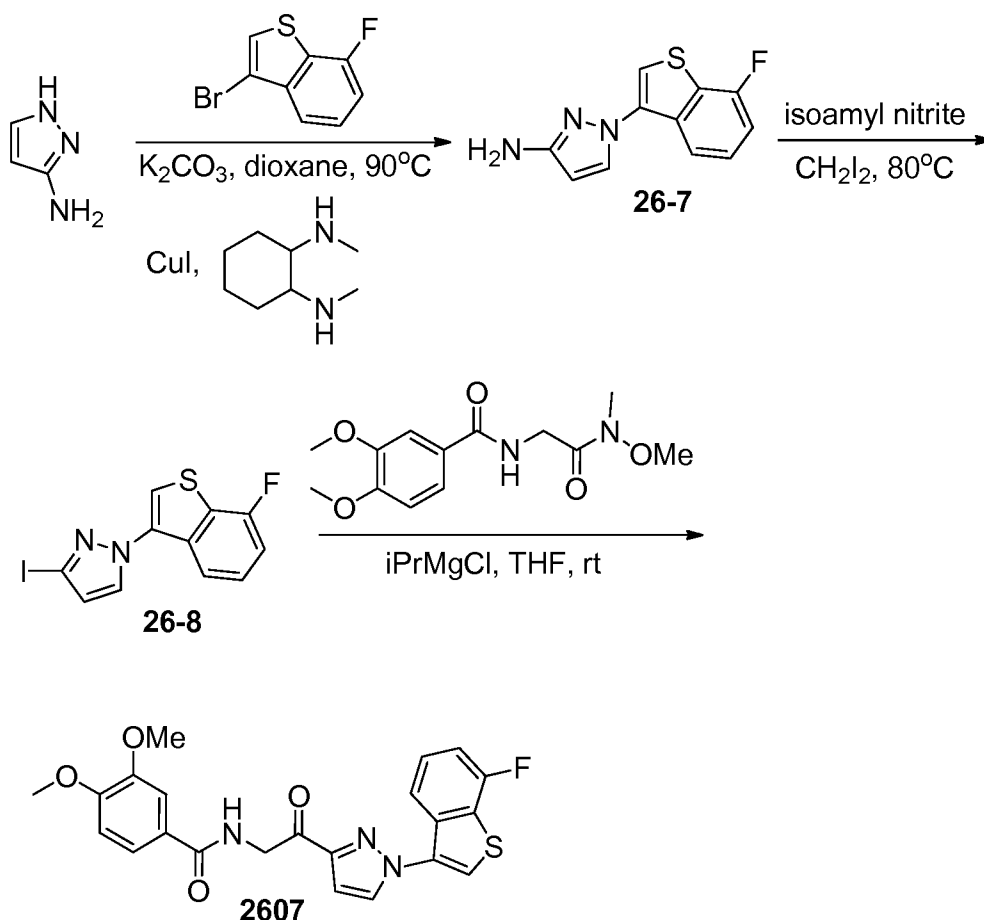


[1168] Compound **2605** was prepared using 2,6-dichloro-4-(trifluoromethyl)pyridine and by following a synthetic route, which closely follows that described for preparation of compound **2604**. LCMS: 519.1 m/z $[M+H]^+$.



[1169] Compound **2606** was prepared using 3,6-dichloropyridazine and by following a synthetic route, which closely follows that described for preparation of compound **2605**. LCMS: 452.05 m/z $[M+H]^+$.

EXAMPLE 26-2
Preparation of Compound 2607

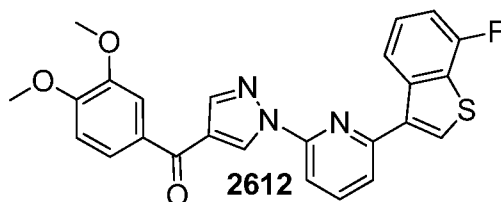


[1170] To a stirring mixture of 1H-pyrazol-3-amine (250 mg, 3 mmol) in dioxane (2 mL, deoxygenated prior to use) were added CuI (115 mg, 0.6 mmol), N1,N2-dimethylcyclohexane-1,2-diamine (102 mg, 0.72 mmol), K_2CO_3 (1.2 g, 9.04 mmol), and 3-bromo-7-fluorobenzo[b]thiophene (580 mg, 2.51 mmol). The mixture was heated at reflux for 2 h and then cooled to rt. The mixture was diluted with EtOAc and quenched with 10% NH_4OH . 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 by silica column chromatograph to afford **26-7** as a yellow solid (240 mg, 55% yield). LC/MS: 234.14 m/z $[M+H]^+$.

[1171] To a stirring mixture of **26-7** (180 mg, 0.77 mmol) in CH_2I_2 (3 mL) was added isoamyl nitrite (888 mg, 7.7 mmol). The mixture was stirred at 80°C for 1 h and then cooled to rt. The crude mixture was concentrated under reduced pressure. The crude

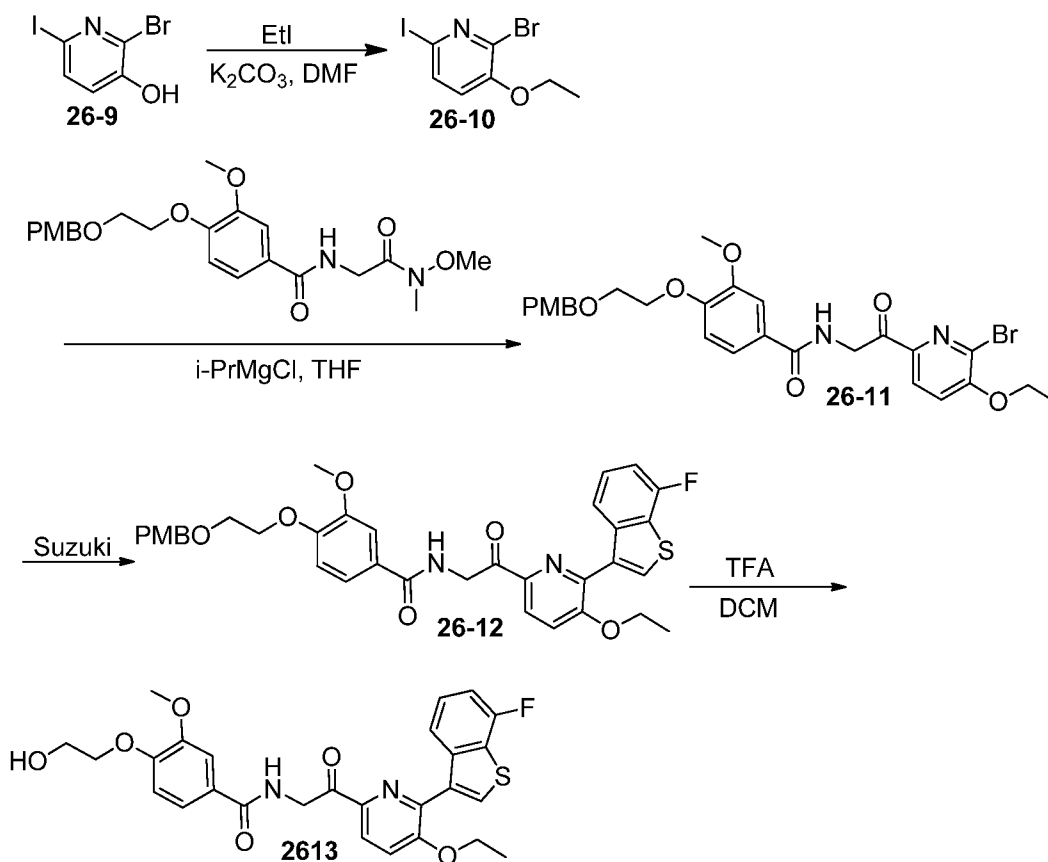
product was purified via silica column chromatograph to afford **26-8** as a yellow oil (230 mg). LCMS: 345.05 m/z [M+H]⁺.

[1172] To a stirring mixture of 3,4-dimethoxy-N-(2-(methoxy(methyl)amino)-2-oxoethyl)benzamide (62 mg, 0.21 mmol) and **26-8** (80 mg, 0.26 mmol) in THF at rt under argon was added a solution of iPrMgCl in THF (0.35 mL, 0.65 mmol). The mixture was stirred at rt for 20 mins and then diluted with EtOAc. The reaction was slowly quenched with a saturated NH₄Cl solution. The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column and the product mixture was further purified via prep-HPLC to afford compound **2607** as a yellow solid. LCMS: 440.25 m/z [M+H]⁺.



[1173] Compound **2612** was prepared using 2,6 dichloro pyridine and by following a synthetic route, which closely follows that described for preparation of compound **2607**. LCMS: 460.05 m/z [M+H]⁺.

EXAMPLE 26-3
Preparation of Compound 2613

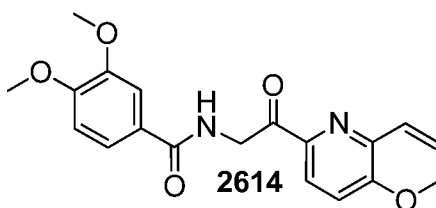


[1174] To a solution of **26-9** (300 mg, 1.0 mmol) in DMF (4 mL) was added K_2CO_3 (276 mg, 2.0 mmol) and EtI (163 mg, 1.05 mmol). The mixture was stirred at rt for 1 h and then diluted with EtOAc. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column to afford **26-10** as a white solid. LCMS: 327.80 m/z $[M+H]^+$.

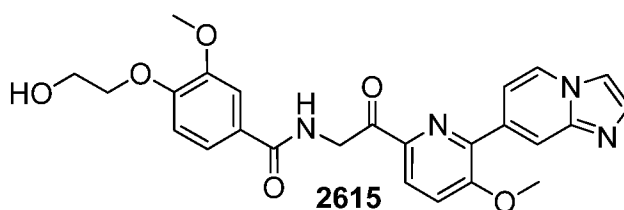
[1175] To a solution of **26-10** (91 mg, 0.28 mmol) and 3-methoxy-N-(2-(methoxy(methyl)amino)-2-oxoethyl)-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzamide (80 mg, 0.18 mmol) in THF (0.28 mL) was added a solution of $i\text{-PrMgCl}$ (0.28 mL, 0.56 mmol) in THF in portions. The mixture was reacted for 15 mins and slowly quenched with a saturated NH_4Cl solution and extracted with EA. The organic phase was dried over sodium sulfate, and then concentrated in vacuum to give crude **26-11**, which was purified by column chromatography to give purified **26-11** (45 mg). LCMS: 573.0 m/z $[M+H]^+$.

[1176] To a solution of **26-11** (70 mg, 0.122 mmol) in dioxane/H₂O (10 : 1) (1.65 mL) were added a benzo-thiophene-based boronic ester (34 mg, 0.122 mmol), Pd(dppf)Cl₂ (25 mg, 0.025 mmol) and KOAc (35 mg, 0.36 mmol). The mixture stirred at 120°C for 1 h under microwave conditions. The mixture was cooled to rt and concentrated under reduced pressure. The crude mixture was purified by column chromatography to give **26-12** as a yellow oil. LCMS: 645 m/z [M+H]⁺.

[1177] To a stirring mixture of **26-12** (20 mg) in DCM (1.0 mL) at rt was added TFA (0.1 mL). The mixture was stirred for 5 mins, diluted with EtOAc and slowly quenched with a cold saturated NaHCO₃ solution, until pH >7. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by prep-HPLC to afford compound **2613** as a white solid. LCMS: 525.10 m/z [M+H]⁺.

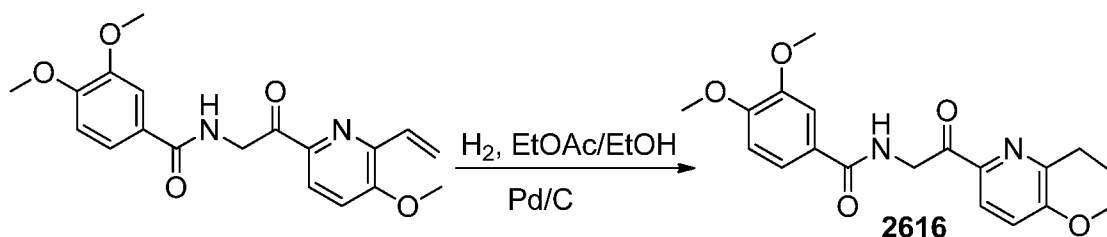


[1178] Compound **2614** was prepared using N-(2-(6-bromo-5-methoxypyridin-2-yl)-2-oxoethyl)-3,4-dimethoxybenzamide and vinyl boronic ester, and by following a synthetic route, which closely follows that described for preparation of compound **2613**. LCMS: 357.10 m/z [M+H]⁺.

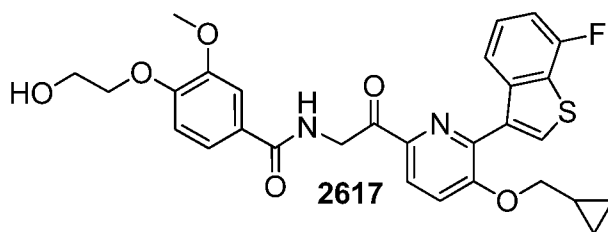


[1179] Compound **2615** was prepared using N-(2-(6-bromo-5-ethoxypyridin-2-yl)-2-oxoethyl)-3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzamide with 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine followed by the removal of PMB ether, and by following a synthetic route, which closely follows that described for preparation of compound **2613**. LCMS: 477.15 m/z [M+H]⁺.

EXAMPLE 26-4
Preparation of Compound 2616

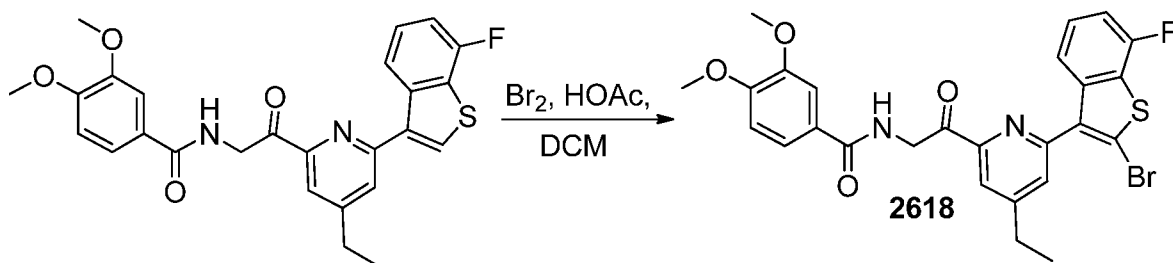


[1180] To a stirring mixture of 3,4-dimethoxy-N-(2-(5-methoxy-6-vinylpyridin-2-yl)-2-oxoethyl)benzamide (10 mg, 0.028 mmol) in EtOAc/EtOH (5 mL/1.0 mL) was added Pd/C (5 mg). The mixture was placed under hydrogen balloon and stirred for 20 mins. The crude mixture was filtered through a plug of celite and the plug was washed several times with EtOAc (2 x 10 mL). The mixture was concentrated under reduced pressure and purified via prep-HPLC to afford compound **2616** as a white solid. LCMS: 359.10 m/z [M+H]⁺.



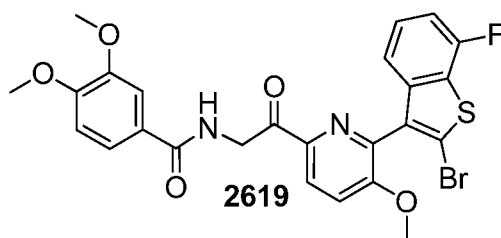
[1181] Compound **2617** was prepared using 2-bromo-6-iodopyridin-3-ol and (bromomethyl)cyclopropane were used as starting materials for the first alkylation step, and by following a synthetic route, which closely follows that described for preparation of compound **2613**. LCMS: 551.10 m/z [M+H]⁺.

EXAMPLE 26-5
Preparation of Compound 2618



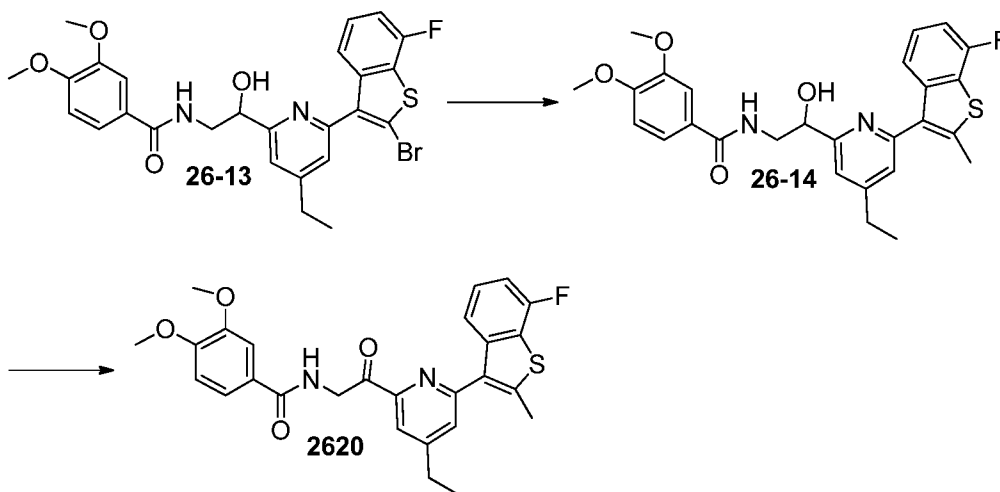
[1182] To a stirring mixture N-(2-(4-ethyl-6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)-2-oxoethyl)-3,4-dimethoxybenzamide (30 mg, 0.06 mmol) in HOAc (0.5 mL) at rt was added a solution of bromine (20 mg) in DCM (0.25 mL). The mixture was

stirred at rt until the starting material was consumed. The mixture was diluted with EtOAc and slowly quenched with $\text{Na}_2\text{S}_2\text{O}_3$. 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 prep-HPLC to afford compound **2618** as a white solid. LCMS: 557.0 m/z $[\text{M}+\text{H}]^+$.



[1183] Compound **2619** was prepared using N-(2-(6-(7-fluorobenzo[b]thiophen-3-yl)-5-methoxypyridin-2-yl)-2-oxoethyl)-3,4-dimethoxybenzamide and bromine in DCM in the presence of HOAc, and by following a synthetic route, which closely follows that described for preparation of compound **2618**. LCMS: 559.0 m/z $[\text{M}+\text{H}]^+$.

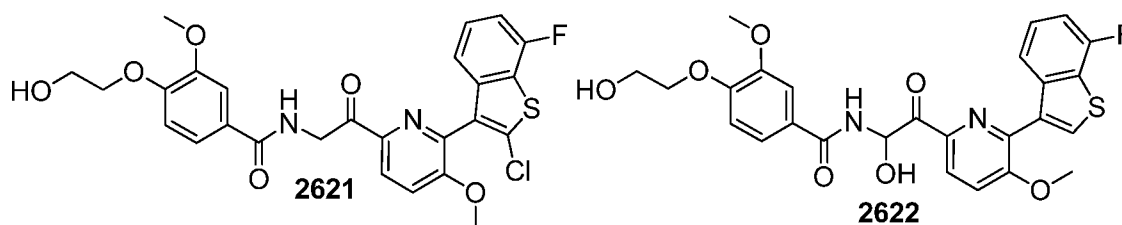
EXAMPLE 26-6
Preparation of Compound 2620



[1184] To a stirring mixture of **26-13** (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 rt, diluted with EtOAc and slowly quenched with a saturated NH_4Cl solution. The mixture was stirred at rt for 20 mins and then the layers were separated. The aqueous layer was extracted with EtOAc. The organic

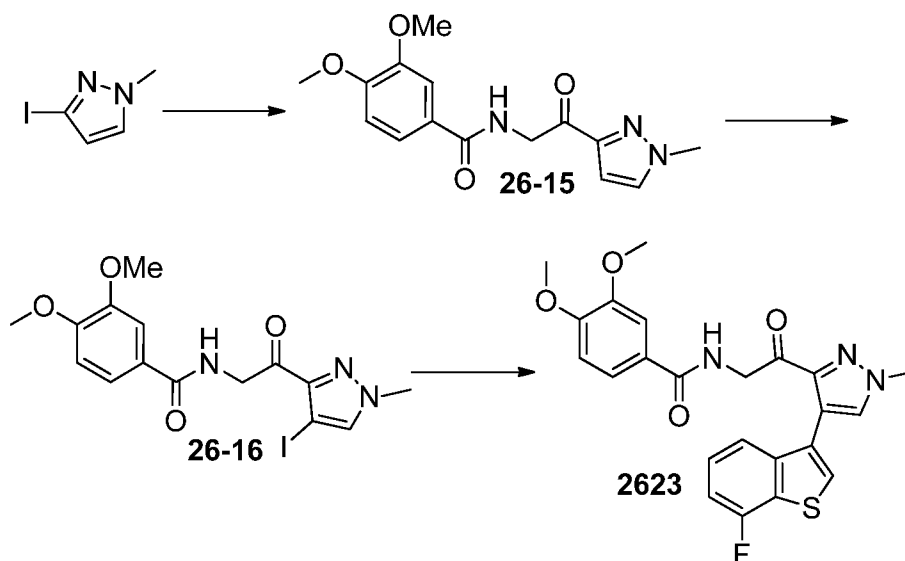
layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product mixture was purified via silica gel column to afford **26-14** as a colorless oil. LCMS: 495.1 m/z $[\text{M}+\text{H}]^+$.

[1185] To a stirring mixture of **26-14** (18 mg, 0.036) in DCM (2 mL) at rt was added Dess–Martin periodinane (154 mg, 0.36 mmol). The mixture was stirred at rt for 1 h and then slowly quenched with 5% NaHSO_3 and a saturated 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 mixture was purified using prep-HPLC to afford compound **2620** as a white solid. LCMS: 493.15 m/z $[\text{M}+\text{H}]^+$.



[1186] To a stirring mixture of N-(2-(6-(7-fluorobenzo[b]thiophen-3-yl)-5-methoxypyridin-2-yl)-2-oxoethyl)-4-(2-hydroxyethoxy)-3-methoxybenzamide (40 mg, 0.67 mmol) in THF/water (0.5 mL/0.05 mL) at rt was added NCS (27 mg, 2 mmol). The mixture was heated at 70°C for 1 h and then quenched with a saturated NaHCO_3 . The mixture was diluted with EtOAc and 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 prep-HPLC to afford compounds **2621** and **2622**. Compound **2621**: LCMS: 545.10 m/z $[\text{M}+\text{H}]^+$. Compound **2622**: LCMS: 527.1 m/z $[\text{M}+\text{H}]^+$.

EXAMPLE 26-7
Preparation of Compound 2623

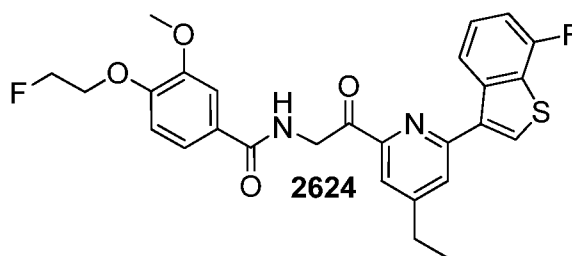


[1187] To a stirring mixture of 3-iodo-1-methyl-1H-pyrazole (250 mg, 0.96 mmol) and 3,4-dimethoxy-N-(2-(methoxy(methyl)amino)-2-oxoethyl)benzamide (220 mg, 0.8 mmol) in THF was added a solution of *i*-PrMgCl (1.7 mL, 3.36 mmol) in THF (2.0M). The mixture was stirred for 20 mins, diluted with EtOAc and slowly quenched with a saturated NH₄Cl solution. The mixture was stirred at rt for 20 mins and the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product mixture was purified via silica gel column to afford **26-15** as a white solid (160 mg). LCMS: 304.1 m/z [M+H]⁺.

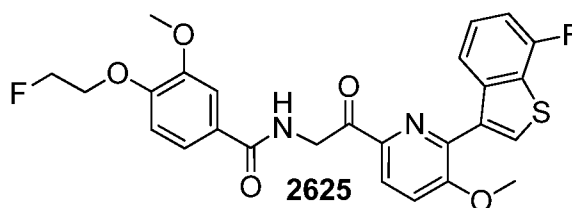
[1188] To a stirring mixture of **26-15** (160 mg, 0.37 mmol) in CH₃CN in a presence of TFA (0.01 mL) was added NIS (130 mg, 0.59 mmol). The mixture was heated at 60°C for 2 h and then cooled to rt. The mixture was stirred for 20 mins, diluted with EtOAc and quenched with a saturated NaHCO₃ solution. The mixture was stirred at rt for 20 mins and the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude mixture was purified via silica gel chromatography to afford **26-16** as a white solid. LCMS: 430.0 m/z [M+H]⁺.

[1189] To a stirring mixture of **26-16** (40 mg, 0.093 mmol) in dioxane/water (10:1, 1.5 mL total volume) were added 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-

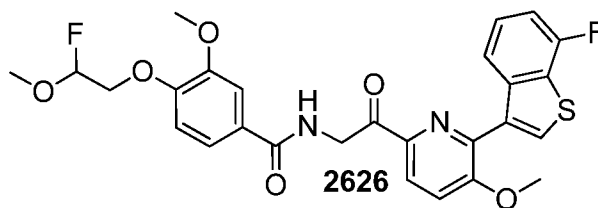
tetramethyl-1,3,2-dioxaborolane (30 mg, 0.1 mmol), PdCl₂(dppf) (12 mg, 0.014 mmol), and KOAc (32 mg, 0.33 mmol). The mixture was heated at 100°C for 2 h. The mixture was cooled to rt and concentrated under reduced pressure. The crude product mixture was purified via silica gel chromatography and further purified via prep-HPLC to afford compound **2623** as a white solid. LCMS: 454.1 m/z [M+H]⁺.



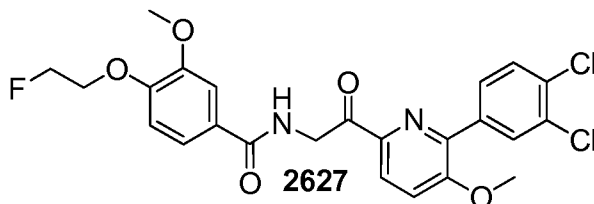
[1190] To a stirring mixture of N-(2-(4-ethyl-6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)-2-oxoethyl)-4-(2-hydroxyethoxy)-3-methoxybenzamide (10 mg, 0.02 mmol) was added DAST (16 mg, 0.1 mmol) at 0°C. The mixture was reacted at 0°C for 1 h and then warmed to rt for 5 mins. The mixture was diluted with EtOAc and slowly quenched with a cold saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc. The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product mixture was purified via prep-HPLC to afford compound **2624** as a white solid. LCMS: 511.15 m/z [M+H]⁺.



[1191] Compound **2625** was prepared using N-(2-(6-(7-fluorobenzo[b]thiophen-3-yl)-5-methoxypyridin-2-yl)-2-oxoethyl)-4-(2-hydroxyethoxy)-3-methoxybenzamide and by following a synthetic route, which closely follows that described for preparation of compound **2624**. LCMS: 513.10 m/z [M+H]⁺.



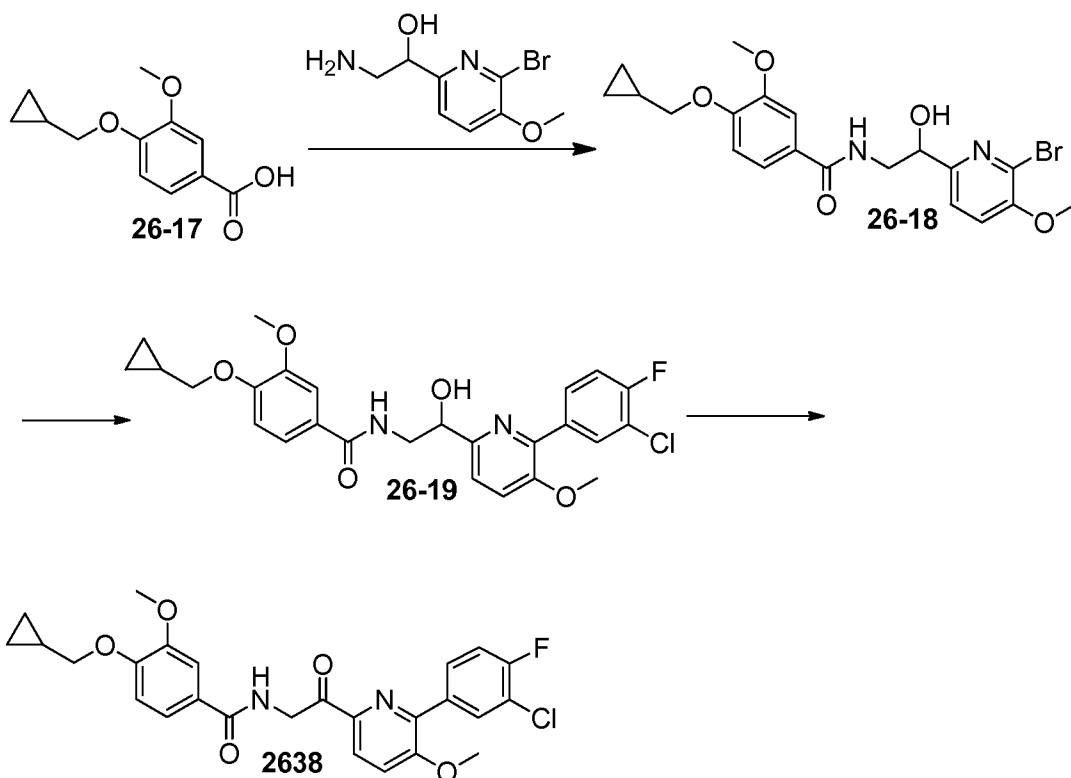
[1192] Compound **2626** was prepared using N-(2-(6-(7-fluorobenzo[b]thiophen-3-yl)-5-methoxypyridin-2-yl)-2-oxoethyl)-4-(2-hydroxy-2-methoxyethoxy)-3-methoxybenzamide and by following a synthetic route, which closely follows that described for preparation of compound **2624**. LCMS: 543.15 m/z [M+H]⁺.



[1193] Compound **2627** was prepared using N-(2-(6-(3,4-dichlorophenyl)-5-methoxypyridin-2-yl)-2-oxoethyl)-4-(2-hydroxyethoxy)-3-methoxybenzamide with DASF in DCM, and by following a synthetic route, which closely follows that described for preparation of compound **2624**. LCMS: 507.05 m/z [M+H]⁺.

EXAMPLE 26-8

Preparation of Compound 2638

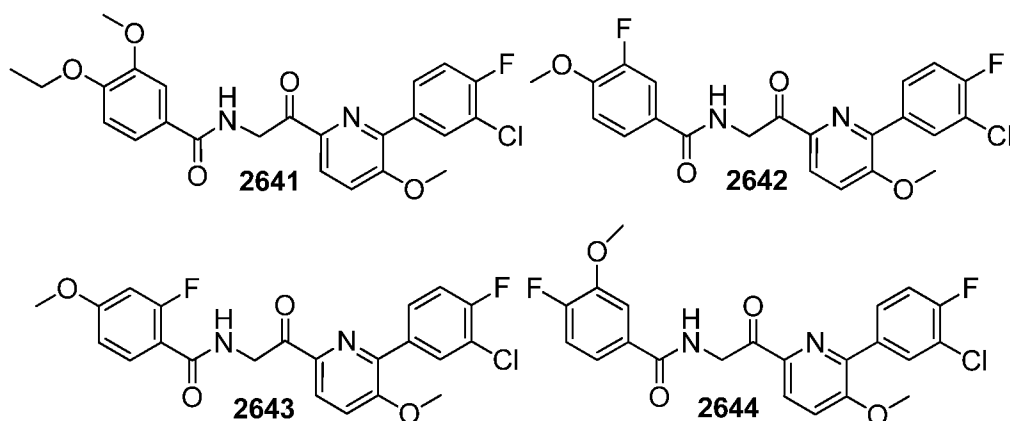


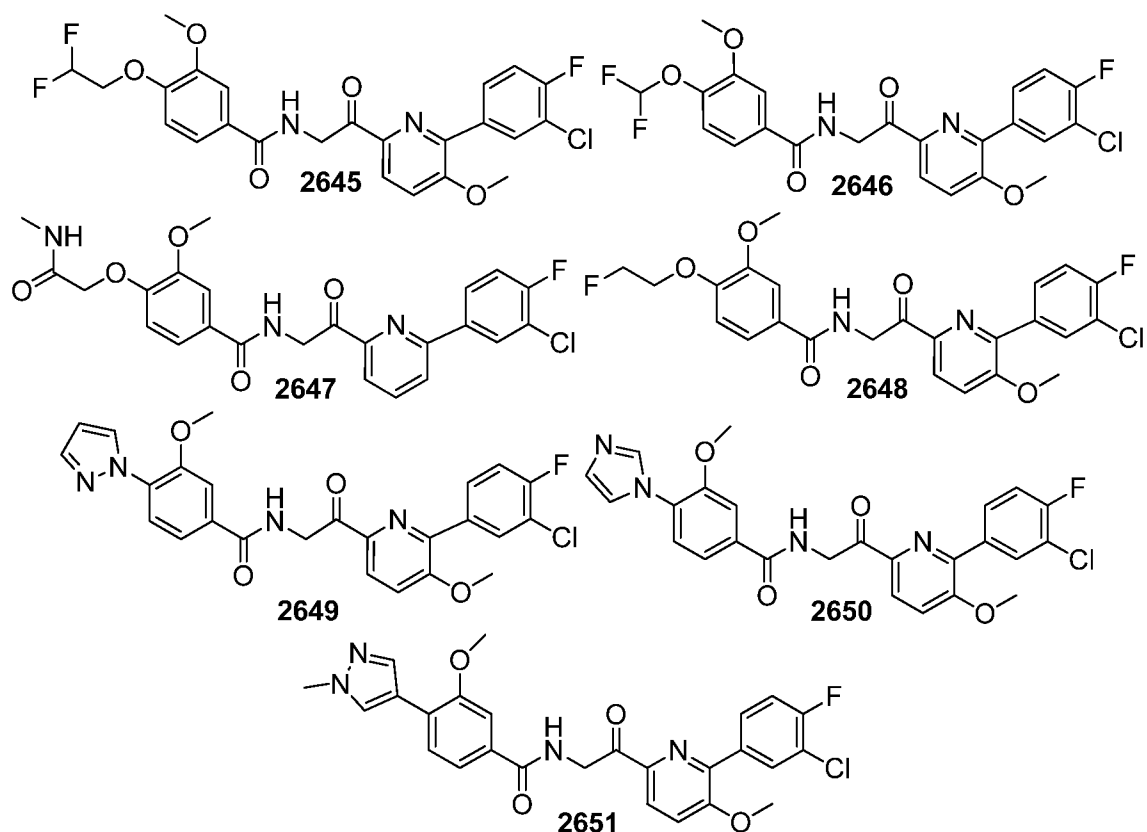
[1194] To a stirring mixture of **26-17** (44 mg, 0.197 mmol) in DMF were added HATU (83 mg, 0.218 mmol) and DIPEA (51 mg, 0.4 mmol). The mixture was stirred at rt for 10 min and a solution of 2-amino-1-(6-bromo-5-methoxypyridin-2-yl)ethan-1-ol was

added. The mixture was stirred at rt for 1 h, diluted with EtOAc and quenched with a saturated NaHCO_3 solution. The mixture was stirred at rt 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 **26-18**. LCMS: 451.05 m/z $[\text{M}+\text{H}]^+$.

[1195] To a stirring mixture of **26-18** (28 mg, 0.062 mmol) in DME/water (10:1, 2.2 mL) were added Cs_2CO_3 (60 mg, 0.19 mmol), PdCl_2dppf (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 rt and concentrated under reduced pressure. The crude mixture was purified via silica gel chromatography to afford **26-19**. LCMS: 501.15 m/z $[\text{M}+\text{H}]^+$.

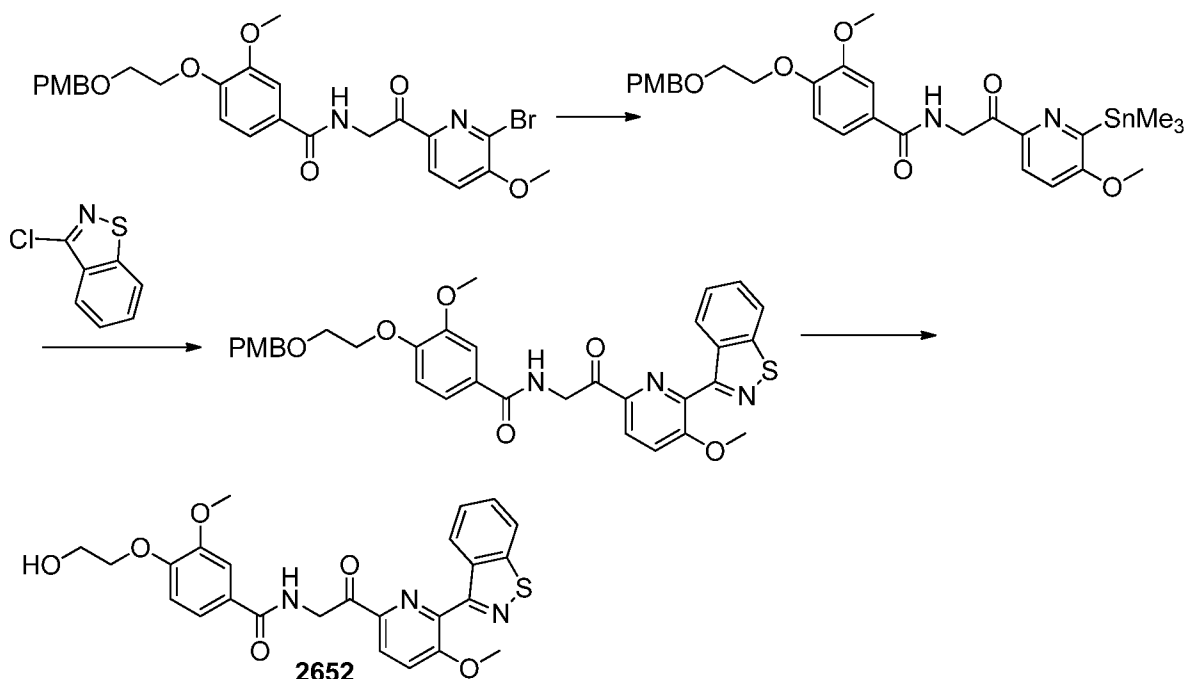
[1196] To a stirring mixture of **26-19** (30 mg, 0.06 mmol) in DCM (2 mL) at rt was added Dess–Martin periodinane (400 mg, 0.9 mmol). The mixture was stirred at rt for 1 h and then slowly quenched with 5% NaHSO_3 and a saturated NaHCO_3 solution. The aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product mixture was purified using prep-HPLC to afford compound **2638** as a white solid. LCMS: 499.15 m/z $[\text{M}+\text{H}]^+$.





[1197] Compounds **2641**, **2642**, **2643**, **2644**, **2645**, **2646**, **2647**, **2648**, **2649**, **2650** and **2651** 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 compound **2638**. Compound **2641**: LCMS: 473.10 m/z [M+H]⁺. Compound **2642**: LCMS: 447.05 m/z [M+H]⁺. Compound **2643**: LCMS: 447.05 m/z [M+H]⁺. Compound **2644**: LCMS: 447.05 m/z [M+H]⁺. Compound **2645**: LCMS: 509.05 m/z [M+H]⁺. Compound **2646**: LCMS: 495.10 m/z [M+H]⁺. Compound **2647**: LCMS: 486.05 m/z [M+H]⁺. Compound **2648**: LCMS: 491.05 m/z [M+H]⁺. Compound **2649**: LCMS: 495.05 m/z [M+H]⁺. Compound **2650**: LCMS: [M+H] 495.05. Compound **2651**: LCMS: [M+H] 509.1.

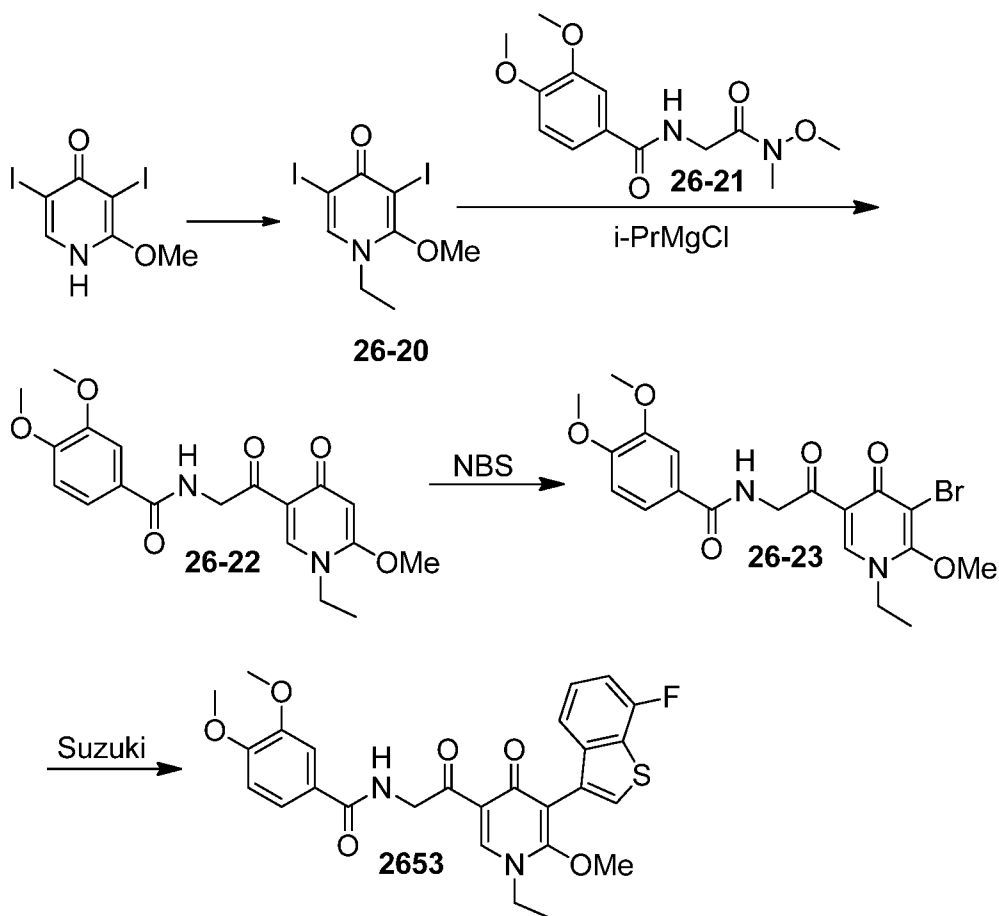
EXAMPLE 26-9
Preparation of Compound 2652



[1198] To a stirring mixture of N-(2-(6-bromo-5-methoxypyridin-2-yl)-2-oxoethyl)-3-methoxy-4-((2-((4-methoxybenzyl)oxy)ethoxy)benzamide (80 mg, 0.14 mmol) in dioxane (2 mL, deoxygenated prior to use) were added copper (I) thiophene carboxylate (5 mg), Pd(PPh₃)₄ (35 mg, 0.03 mmol), and Me₆Sn₂ (80 mg, 0.28 mmol). The mixture was heated under microwave irradiation for 1 h at 110°C. The mixture was cooled to rt and the crude mixture was filtered through a plug of celite. The plug was washed with EtOAc. The filtrate was concentrated under reduced pressure and used in the next step without further purification. LCMS: 645.1 m/z [M+H]⁺.

[1199] The crude stannane intermediate was dissolved in dioxane (1.0 mL). Copper (I) thiophene carboxylate (5 mg), Pd(PPh₃)₄ (35 mg, 0.03 mmol) and 3-chlorobenzo[d]isothiazole (48 mg, 0.48 mmol) was added. The mixture was heated at 90°C for 1 h and then cooled to rt. This mixture was directly loaded into a silica gel column to afford the PMB protected ether. The PMB ether was removed using TFA in DCM at rt to afford compound **2652**. LCMS: 494.05 m/z [M+H]⁺.

EXAMPLE 26-10
Preparation of Compound 2653



[1200] To a stirring mixture of 3,5-diiodo-2-methoxypyridin-4(1H)-one (380 mg, 1 mmol) in DMF (3 mL) were added K_2CO_3 (301 mg, 2.2 mmol) and ethyl iodide (0.12 mL, 1.51 mmol). The mixture was stirred at 75°C for 2 h and then cooled to rt. The mixture was diluted with EtOAc and washed with a saturated NaCl solution. The aqueous layer was washed with EtOAc (2 x 20 mL). 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 **26-20** as a white solid. LCMS: 406.0 m/z $[M+H]^+$.

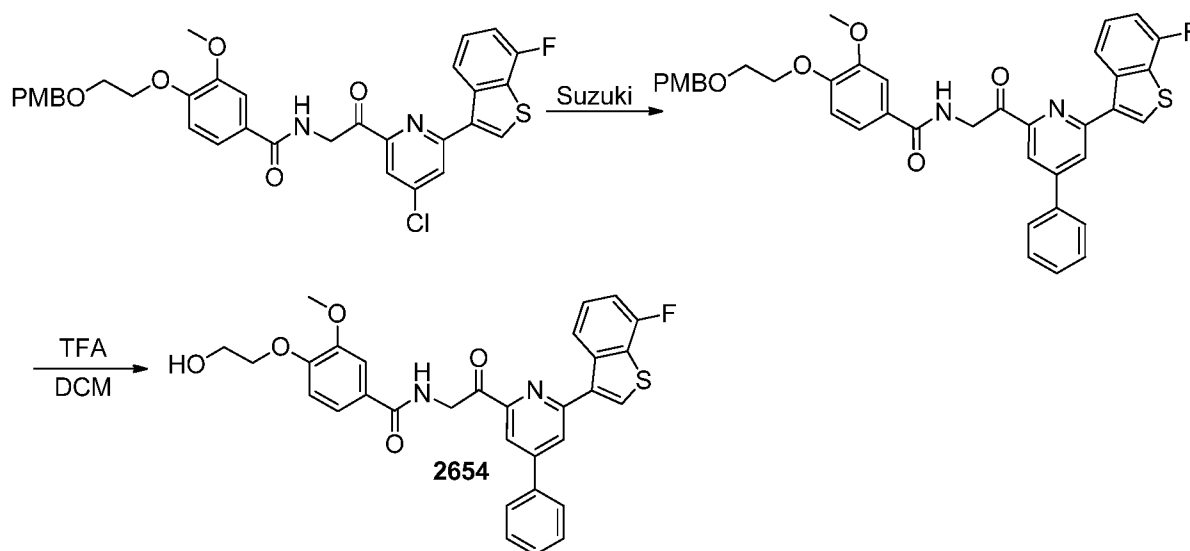
[1201] To a stirring mixture of **26-20** (130 mg, 0.32 mmol) and **26-21** (55mg, 0.19 mmol) in THF at rt was added a solution of *i*PrMgCl in THF (0.48 mL, 0.95 mmol). The mixture was stirred at rt for 10 mins, diluted with EtOAc and quenched slowly with a saturated NH_4Cl solution. The organic layers were dried (Na_2SO_4), filtered and concentrated

under reduced pressure. The crude product mixture was purified via silica gel chromatography to afford **26-22** (55 mg, 73%) as a white solid. LCMS: 375.1 m/z [M+H]⁺.

[1202] To a stirring mixture of **26-22** (55 mg, 0.147 mmol) in DMF (0.5 mL) at rt was added NBS (78.5 mg, 0.44 mmol). The mixture was stirred at 70°C for 15 mins, cooled to rt and diluted with EtOAc. The reaction was quenched with a saturated NaHCO₃ solution. The aqueous layer was washed with EtOAc (2 x 20 mL). The organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified via prep-HPLC to afford **26-23** (20 mg) as a white product. LCMS: 453.0 m/z [M+H]⁺.

[1203] To a stirring mixture **26-23** (20 mg, 0.044 mmol) in dioxane/water (10:1, 2.2 mL total volume) were added 2-(7-fluorobenzo[b]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15 mg, 0.054 mmol), PdCl₂(dppf) (13 mg, 0.018 mmol), KOAc (13 mg, 0.132 mmol). The mixture was heated under microwave irradiation for 1 h at 110°C. The mixture was cooled to rt and concentrated under reduced pressure. The crude product mixture was purified via silica gel chromatography and further purified via prep-HPLC to afford compound **2653** (2.6 mg) as a white solid. LCMS: 525.1 m/z [M+H]⁺.

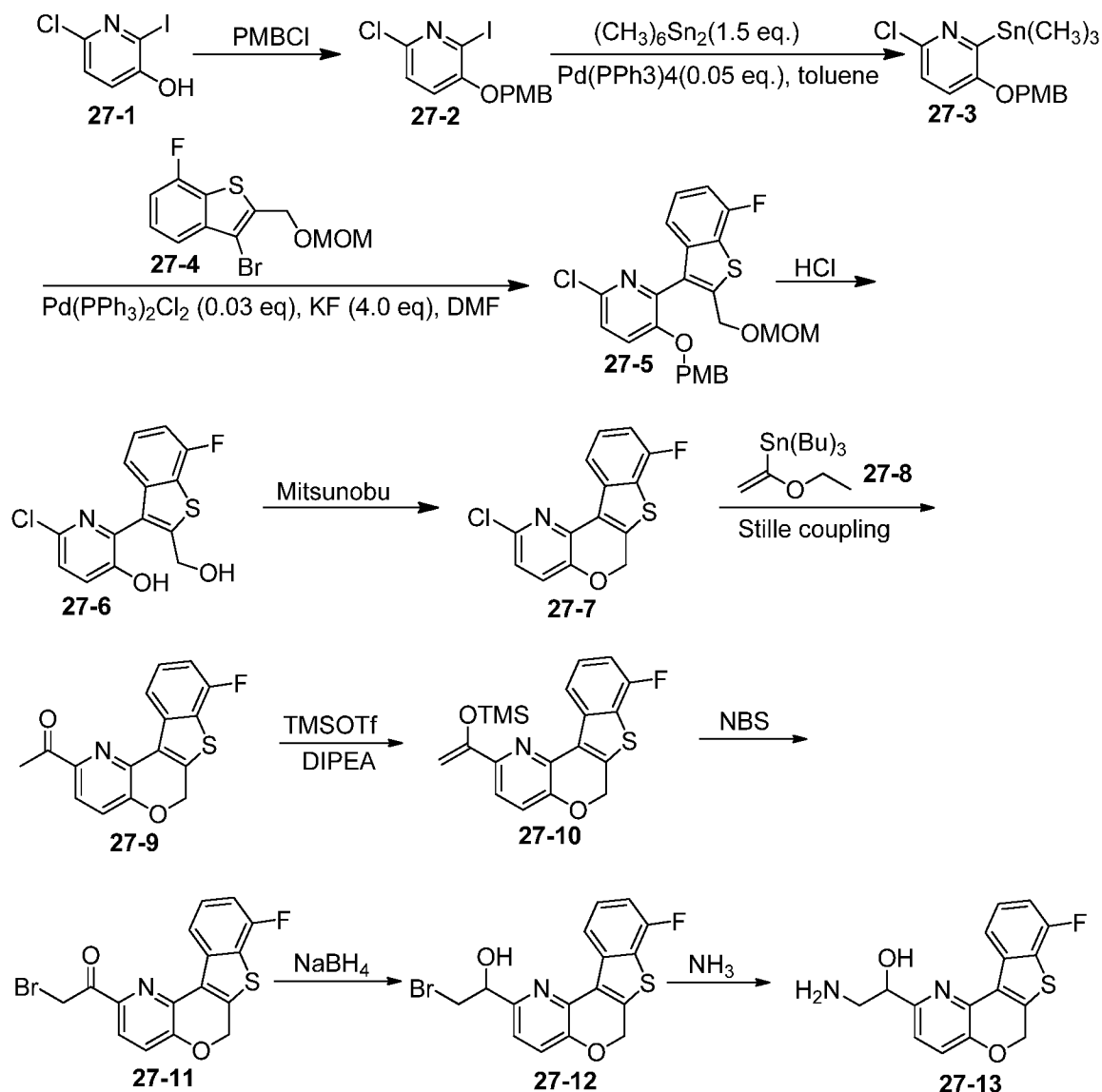
EXAMPLE 26-11 **Preparation of Compound 2654**

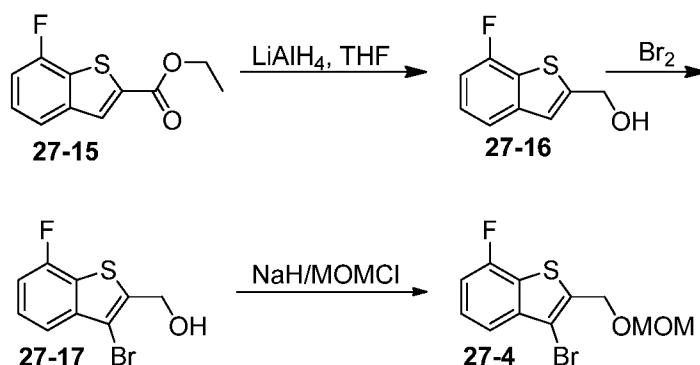


[1204] To a stirring mixture of N-(2-(4-chloro-6-(7-fluorobenzo[b]thiophen-3-yl)pyridin-2-yl)-2-oxoethyl)-3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzamide (30 mg, 0.044 mmol) in dioxane/water (10:1: 2.2 mL total volume) were added PdCl₂(dppf) (7.3 mg, 0.01 mmol), KOAc (17 mg, 0.176 mmol), and phenyl boronic acid (11 mg, 0.088 mmol).

The mixture was stirred was heated under microwave irradiation for 1 h at 110°C. The mixture was cooled to rt and concentrated under reduced pressure. The crude product mixture was purified via silica gel chromatography to afford the PMB ether. The PMB ether was removed using TFA in DCM at rt. The crude product was concentrated under reduced pressure and purified via prep-HPLC to afford compound **2654** (2.6 mg) as a white solid. LCMS: 557.15 m/z [M+H]⁺.

EXAMPLE 27-1
Preparation of Compound 27-13





[1205] To a solution of **27-1** (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 rt overnight. After complete conversion, the reaction was quenched with MeOH and H₂O, and extracted with EA. The organic phase was concentrated to give **27-2** (11 g, 87.2%). +ESI-MS: m/z 375.9 [M+H]⁺.

[1206] To a solution of **27-2** (36 g, 96 mmol) in toluene (400 mL) was added (CH₃)₆Sn₂ (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 **27-3** (22 g). +ESI-MS: m/z 414.0 [M+H]⁺.

[1207] To a solution of **27-15** (30 g, 134 mmol) in anhydrous THF (500 mL) was added LiAlH₄ (7.6 g, 200 mmol) in portions at 0°C, and the mixture was stirred at rt for 2 h (monitored by TLC). The reaction was quenched with a saturated NH₄Cl solution, and extracted with EA to give the crude product, which was purified by column chromatography to give **27-16** (22 g). +ESI-MS: m/z 183.0 [M+H]⁺.

[1208] To a solution of **27-16** (22 g, 121 mmol) in THF (400 mL) was added NBS (25.7 g, 145 mmol), and the mixture was stirred at rt overnight (monitored by TLC). The reaction was quenched with a saturated Na₂S₂O₃ solution, and extracted with EA to give the crude product, which was purified by column chromatography to give **27-17** (23 g). +ESI-MS: m/z 460.9 [M+H]⁺.

[1209] To a solution of **27-17** (22 g, 84.6 mmol) in anhydrous THF (200 mL) was added NaH (8.12 g, 33.85 mmol) in portions at 0°C, and the mixture was stirred at 0°C for 30 mins. MOMCl (27.08 g, 338.5 mmol) was added, and the mixture was stirred at rt 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 **27-4** (21 g). +ESI-MS: m/z 304.9 $[M + H]^+$.

[1210] To a solution of **27-3** (6.36 g, 15.4 mmol) in DMF (50 mL) were added **27-4** (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°C 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 **27-5** (3.8 g). +ESI-MS: m/z 474.1 $[M + H]^+$.

[1211] To a solution of **27-5** (4.5 g, 9.51 mmol) in THF (30 mL) was added 10% HCl (30 mL), and stirred 110°C overnight. The mixture was cooled to rt, and the pH was adjusted to 7.0 by adding a saturated $NaHCO_3$ solution. The mixture was extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give **27-6** (2.0 g), which was used in the next step without purification. +ESI-MS: m/z 310.0 $[M + H]^+$.

[1212] To a solution of **27-6** (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 rt 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 **27-7** (0.7 g). +ESI-MS: m/z 292.0 $[M + H]^+$.

[1213] To a solution of **27-7** (600 mg, 2.06 mmol) in DMF (20 mL) was added **27-8** (1.12 g, 3.10 mmol), KF (494.4 mg, 8.24 mmol) and $Pd(PPh_3)_2Cl_2$ (43.4 mg, 0.062 mmol). The mixture was bubbled with nitrogen gas and stirred at 100°C for 10 h. 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 **27-9** (500 mg). +ESI-MS: m/z 300.0 $[M + H]^+$.

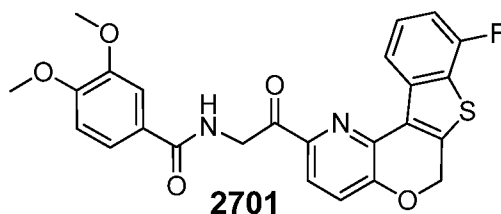
[1214] To a solution of **27-9** (400 mg, 1.34 mmol) in dichloromethane (20 mL) at 0°C was added DIPEA (689.6 mg, 5.36 mmol) and TMSOTf (891.2 mg, 4.01 mmol), and the mixture stirred at 0°C for 30 mins, and then for 1 h at rt. The mixture was diluted with water and extracted with EA. The organic phase was dried over sodium sulfate, and concentrated in vacuum to give crude **27-10**.

[1215] To a solution of crude **27-10** (450 mg) in THF/ H_2O (4:1, 20 mL) was added NBS (212.8 mg, 1.21 mmol) at 0°C, and the mixture was stirred at 0°C for 1 h. The

mixture was extracted with EA. The organic layer was dried over sodium sulfate, and then concentrated in vacuum to give crude product, which was purified by column chromatography to give **27-11** (650 mg). +ESI-MS: m/z 377.9 $[M+H]^+$.

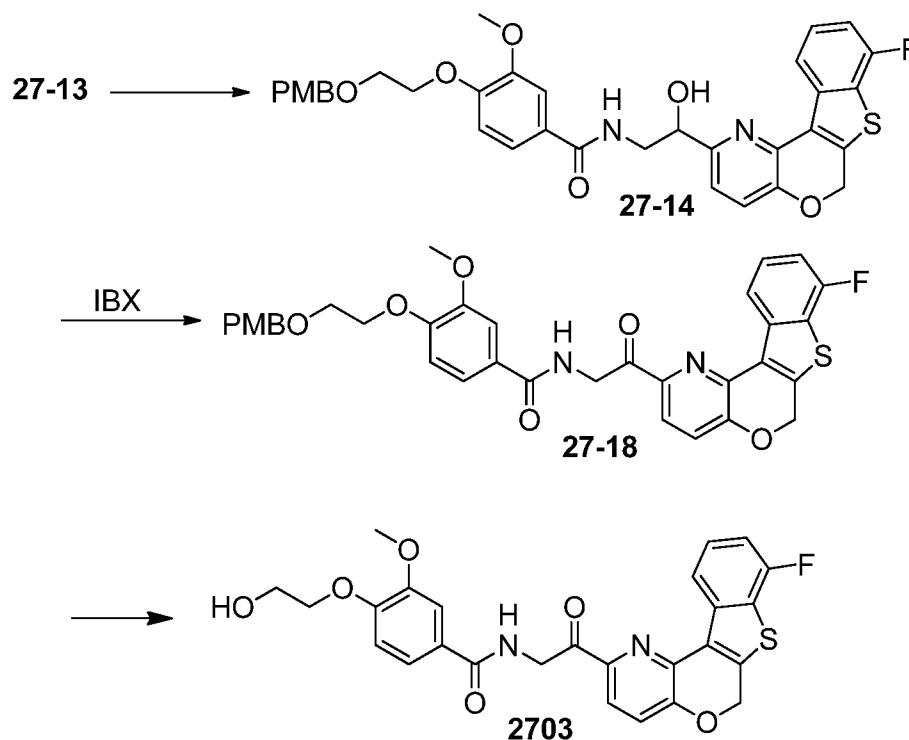
[1216] To a solution of **27-11** (600 mg, 1.6 mmol) in THF (50 mL) was added NaBH_4 (300 mg, 7.96 mmol), and the mixture was stirred at 0°C for 2 mins. The solution was treated with MeOH (5 mL) very slowly for 10 mins (monitored by TLC). The mixture was treated with ice and extracted with EA. The organic layer was dried over sodium sulfate, and concentrated in vacuum to give the crude product, which was purified by column chromatography to give **27-12** (400 mg). +ESI-MS: m/z 379.9 $[M+H]^+$.

[1217] To a solution of **27-12** (400 mg, 1.06 mmol) in EtOH 20 mL was added $\text{NH}_3\cdot\text{H}_2\text{O}$ (10 mL) in a seal tube, and the mixture was stirred at 100°C for 1 h. 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 **27-13** (340 mg). +ESI-MS: m/z 317.1 $[M+H]^+$.



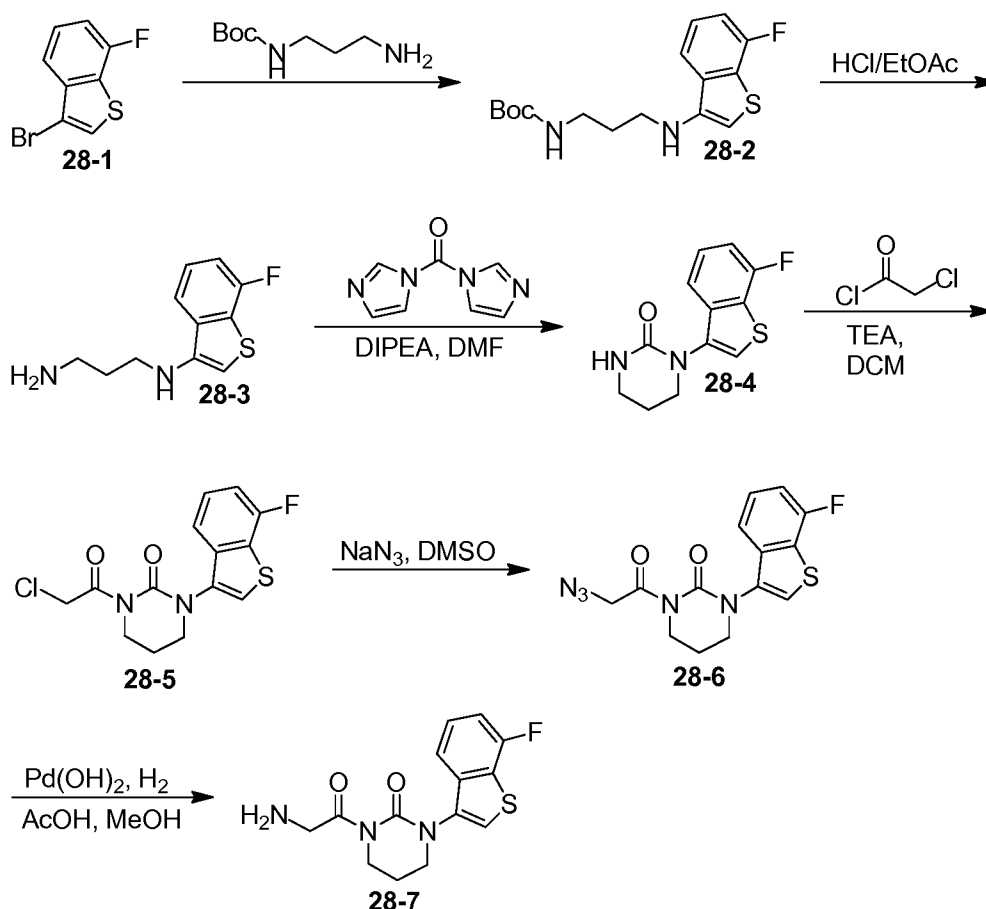
[1218] To a solution of N-(2-(8-fluoro-6H-benzo[4',5']thieno[3',2':4,5]pyrano[3,2-b]pyridin-2-yl)-2-hydroxyethyl)-3,4-dimethoxybenzamide (120 mg, 0.25 mmol) in DMSO (3 mL) was added IBX (210 mg, 0.75 mmol), and stirred at 30°C overnight. The mixture was purified by prep-HPLC to give **2701** (30 mg) as a white solid. +ESI-MS: m/z 479.1 $[M+H]^+$.

EXAMPLE 27-2
Preparation of Compound 2703



[1219] Compound **27-18** (200 mg, 0.318 mmol) was dissolved in TFA/DCM (20 mL), and the mixture was stirred at rt for 1 h (monitored by TLC). The mixture was extracted with EA, and washed with a saturated 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 compound **2703** (28 mg) as a white solid. +ESI-MS: m/z 509.1 $[\text{M} + \text{H}]^+$.

EXAMPLE 28-1
Preparation of Compound 28-7



[1220] Compound **28-1** (10 g, 43.5 mmol), CuI (1.653 g, 8.7 mmol), L-proline (2 g, 17.4 mmol) and K₂CO₃ (9 g, 65.25 mmol) were added to Schleck flask. The flask was evacuated and backfilled with argon, and then degassed DMSO (44 mL) was added. Tert-butyl (3-aminopropyl) carbonate (11.35 g, 65.25 mmol) was added, and the mixture was heated to 80°C until completion. The reaction was quenched with water, and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated at low pressure. The residue was purified by column on silica gel (PE:EA=4:1) to give **28-2** (8.4 g, 59% yield). +ESI-MS: m/z 325.1 [M+H]⁺.

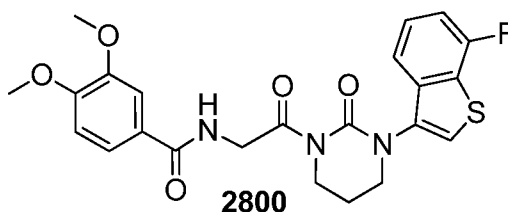
[1221] A round bottom flask was charged with **28-2** (4.6 g, 14.2 mmol) and 4 M HCl in EtOAc (7 mL) was added dropwise. The mixture was stirred at 0°C for 30 mins. The solvent was removed to give crude **28-3** used in next step without further purification,

[1222] To a solution of **28-3** (3.18 g, 14.2 mmol) in DMF (69 mL) was added DIPEA (7.78 g, 56.8 mmol) and CDI (2.53 g, 15.62 mmol). The mixture was stirred at 5°C for 2 h and then heated at 90°C for 10 h. The mixture was extracted with EtOAc and washed with water, dried over Na₂SO₄, and concentrated. The residue was purified by column on silica gel (DCM:MeOH=50:1) to give **28-4** (6 mg, 24%). +ESI-MS: m/z 251.0 [M + H]⁺

[1223] To a solution of **28-4** (1.5 g, 6 mmol) in DCM (30 mL) was added TEA (2.7 mL) and 2-chloroacetyl chloride (1.2 mL, 18 mmol) at 0°C under argon. The reaction was quenched with water, extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by column on silica gel (PE:EA=10:1) to give **28-5** (500 mg, 25%). +ESI-MS: m/z 327.0 [M + H]⁺.

[1224] Compound **28-5** (500 mg, 1.534 mmol) and NaN₃ (398 mg, 6.136 mmol) was added to DMSO (7 mL). The mixture was stirred at 50°C for 2 h. The mixture was extracted with EtOAc, washed with water, dried over Na₂SO₄, and concentrated. The residue was purified by column on silica gel (PE:EA=3:1) to give **28-6** (260 mg, 51%). +ESI-MS: m/z 334.1 [M + H]⁺.

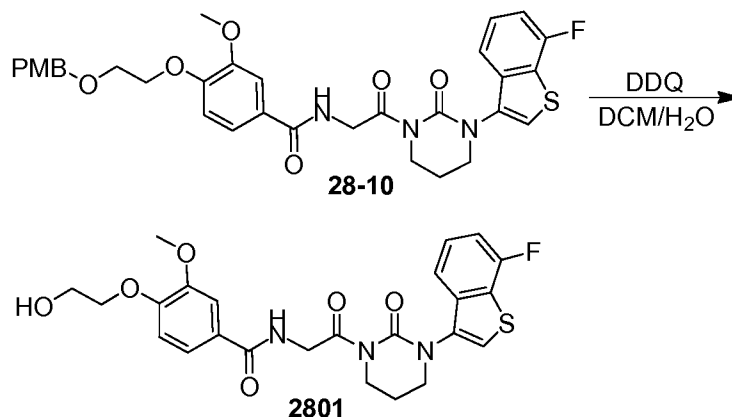
[1225] To a solution of **28-6** (100 mg, 0.3 mmol) in MeOH (5 mL) was added Pd(OH)₂ (6 mL) and one drop of AcOH. The mixture was stirred at rt under H₂ atmosphere for 1 h. The mixture was filtered and the filtrate was dissolved in EtOAc. The solution was washed with aq. NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. Crude **28-7** was used in next step without further purification.



[1226] To a solution of 3,4-dimethoxybenzoic acid (110 mg, 0.6 mmol) in DIPEA (0.2 mL) and DMF (1 mL) was added HATU (230 mg, 0.6 mmol). The mixture was stirred at 40°C for 30 mins. Compound **28-7** (93 mg, 0.3 mmol) was added. The mixture was stirred at 40°C for 10 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The crude

product was purified by prep-HPLC to give compound **2800** (32 mg, 22%). +ESI-MS:m/z 471.8 [M + H]⁺.

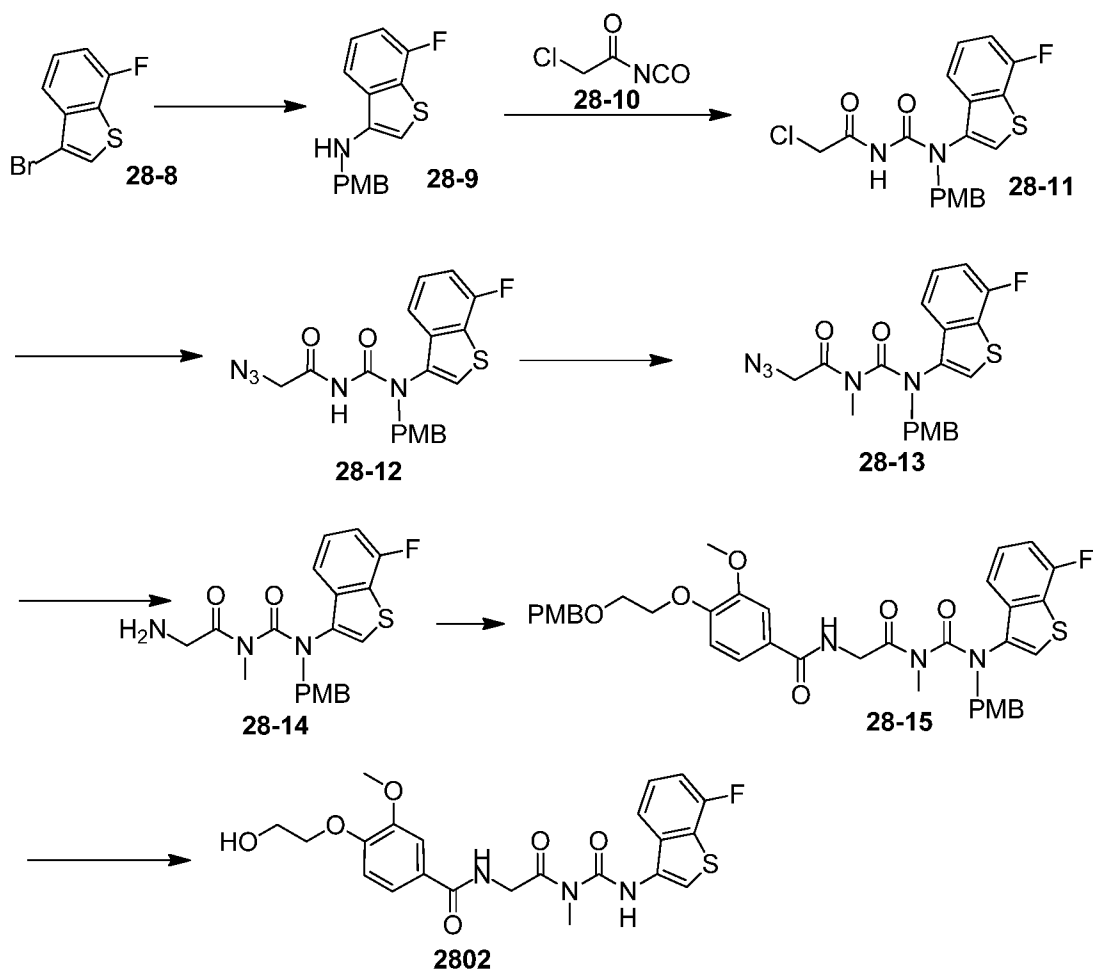
EXAMPLE 28-2
Preparation of Compound 2801



[1227] Compound **28-10** (60 mg, 25%) was prepared using 3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzoic acid and by following a synthetic route, which closely follows that described for preparation of compound **2800**. +ESI-MS:m/z 622.1 [M + H]⁺.

[1228] To a solution of **28-10** (60 mg, 0.1 mmol) in DCM (2 mL) and H₂O (0.2 mL) was added DDQ (45 mg, 0.2 mmol). The mixture was stirred for 2 h. at rt. The mixture was dissolved in DCM (30 mL), and washed with a saturated NaHCO₃ solution. The organic phase was washed with brine, and dried over Na₂SO₄, and concentrated at low pressure. The residue was purified by prep-HPLC to give compound **2801** (12 mg, 25%). +ESI-MS:m/z 501.8 [M + H]⁺.

EXAMPLE 28-3
Preparation of Compound 2802



[1229] Compound **28-8** (10 g, 43.5 mmol), CuI (1.653 g, 8.7 mmol), L-proline (2 g, 17.4 mmol) and K_2CO_3 (9 g, 65.25 mmol) were in a Schlenk flask. The flask was evacuated and backfilled with argon and then degassed DMSO (44 mL) was added. PMBNH₂ (3-aminopropyl)carbamate (12 g, 87.60 mmol) was added and the mixture was heated to 80°C. The reaction was quenched with water, and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column on silica gel (PE:EA=4:1) to give **28-9** (5.5 g, 43 % yield). +ESI-MS: m/z 288.1 $[M+H]^+$.

[1230] A round bottom flask was charged with **28-9** (1.44 g, 5.0 mmol) and THF (10 mL), and **28-10** in THF (7 mL) was added dropwise. The mixture was stirred at 0°C for

30 mins. The solvent was removed to give crude **28-11**, which was used in next step without further purification. +ESI-MS:m/z 406.8 [M +H]⁺.

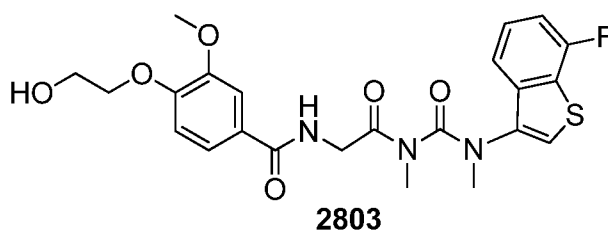
[1231] To a solution of **28-11** (2.03 g, 5.0 mmol) in DMF (10 mL) was added NaN₃ (680 mg, 10.0 mmol), and the mixture was stirred at rt until the starting materials were consumed. The mixture was extracted with EtOAc and washed with water, dried over Na₂SO₄, and concentrated to give **28-12**. +ESI-MS:m/z 414.1 [M +H]⁺

[1232] To a solution of **28-12** (2.07 g, 5 mmol) in DMF (30 mL) was added K₂CO₃ (1.33 g, 10 mmol) and MeI (1.41 g, 10 mmol) at rt. The mixture was stirred at 50°C until the starting materials were consumed. The reaction was quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by column on silica gel (PE:EA=10:1) to give **28-13** (190 mg, 90%). +ESI-MS:m/z 428.1 [M +H]⁺.

[1233] To a solution of **28-13** (85 mg, 0.2 mmol) in MeOH (10 mL) was added Pd/C (10 mg) and one drop of concentrated HCl. The mixture was stirred at room temperature under H₂ atmosphere for 1 h. The mixture was filtered and the filtrate was dissolved in EtOAc. The solution was washed with aq. NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. Crude **28-14** was used in next step without further purification. +ESI-MS:m/z 401.8 [M +H]⁺.

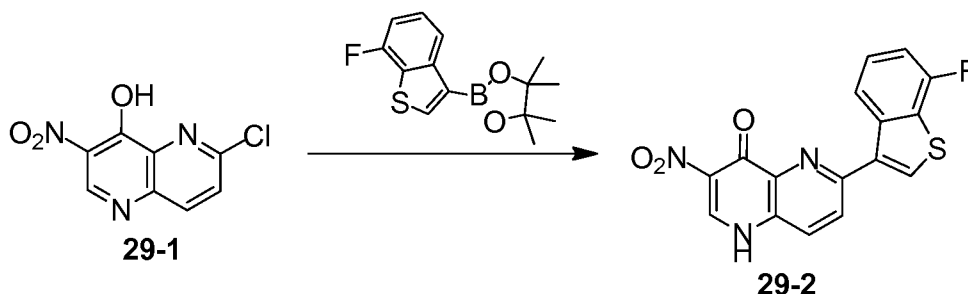
[1234] To a solution of the substituent benzoic acid (66 mg, 0.2 mmol) in DIPEA (0.2 mL) and DMF (5 mL) was added HATU (115 mg, 0.3 mmol). The mixture was stirred at 40°C for 30 mins and then **28-14** (80 mg, 0.2 mmol) was added. The mixture was stirred at 40°C for 1 h. The mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel to give **28-15** (135 mg, 90 %). +ESI-MS:m/z 715.9 [M +H]⁺.

[1235] To a solution of **28-15** (140 mg, 0.2 mmol) in DCM (4 mL) and TFA (2 mL) was added Et₃SiH (1 mL). The mixture was stirred at 0°C for 1 h. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The crude product was purified by prep-HPLC to give compound **2802** (57 mg, 60%). +ESI-MS:m/z 475.8 [M +H]⁺.



[1236] Compound **2803** (57 mg, 60%) was prepared using **28-8** and methylamine hydrochloride, and by following a synthetic route, which closely follows that described for preparation of compound **2802**. +ESI-MS: m/z 489.9 $[M + H]^+$.

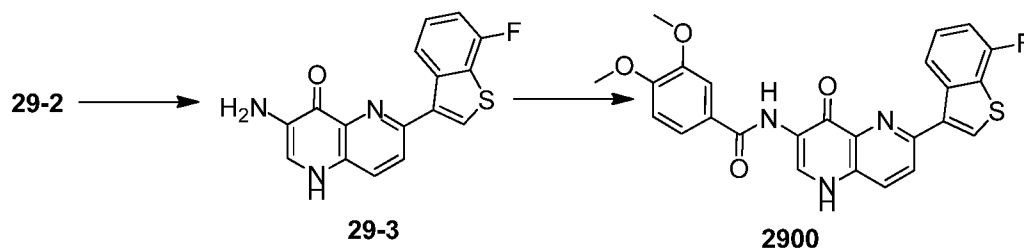
EXAMPLE 29-1
Preparation of Compound 29-2



[1237] Compound **29-1** was prepared according to the procedure in PCT Publication No. 2012/034526, which hereby is incorporated by reference for the limited purpose of preparing **29-1**.

[1238] To a solution of **29-1** (1.6 g, 7.11 mmol) in DMF/H₂O (30 mL) were added the dioxaborolane (1.98 g, 7.11 mmol), and KF (3.7 g, 61.6 mmol) and Pd(PPh₃)₂Cl₂ (150 mg, 0.21 mmol) and K₂CO₃ (1.96 g, 14.22 mmol). The mixture was bubbled with nitrogen gas and stirred at 90°C 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 **29-2** (1.4 g). +ESI-MS: m/z 342.0 $[M + H]^+$.

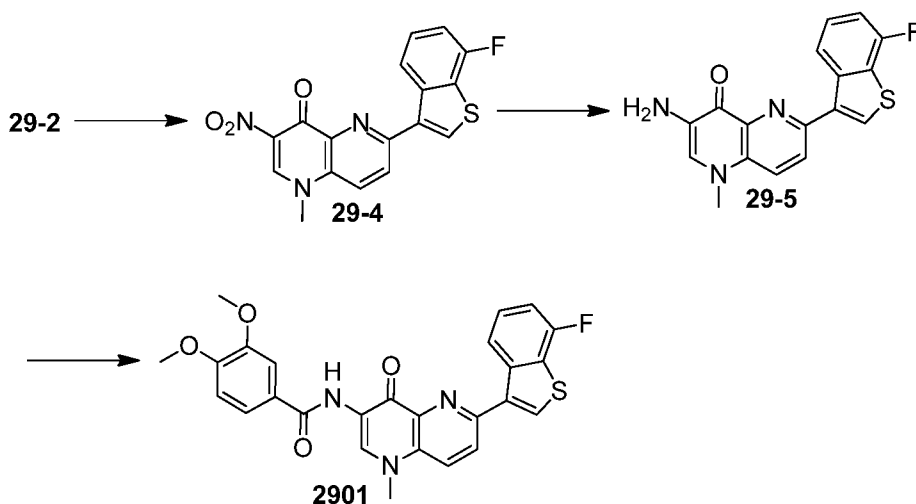
EXAMPLE 29-2
Preparation of Compound 2900



[1239] To a solution of **29-2** (500 mg, 1.47 mmol) in MeOH/DMF (10 mL) was added Pd/C (200 mg), and the mixture was stirred at rt under hydrogen gas balloon for 1 h. The mixture was concentrated in vacuum to give **29-3** (250 mg). +ESI-MS: m/z 312.0[M + H]⁺.

[1240] To a solution of **29-3** (150 mg, 0.48 mmol) in DCM (30 mL) was added Et₃N (97.4 mg, 0.96 mmol) and 3,4-dimethoxybenzoyl chloride (96 mg, 0.48 mmol), and the mixture was stirred at rt for 3 h. The mixture was concentrated in vacuum to give the crude product, which was purified by TLC and prep-HPLC to give compound **2900** (4.0 mg). +ESI-MS: m/z 476.1[M + H]⁺.

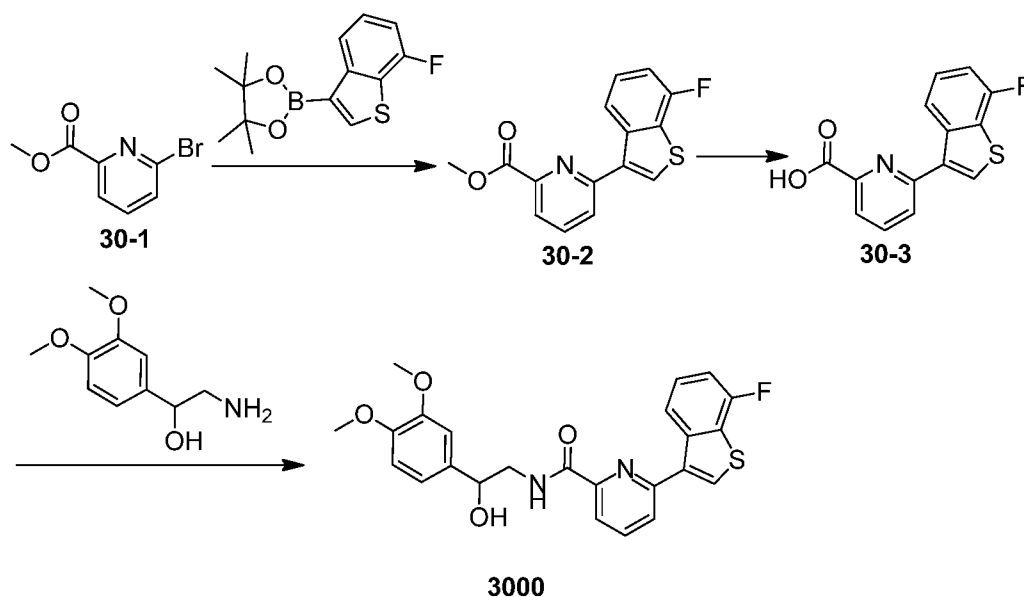
EXAMPLE 29-3 Preparation of Compound 2901



[1241] To a solution of **29-2** (400 mg, 1.17 mmol) in DMF (100 mL) was added K₂CO₃ (684 g, 4.69 mmol) and CH₃I (668 mg, 4.69 mmol), and the mixture was stirred at rt overnight (monitored by LCMS). The mixture was concentrated in vacuum to give the crude product, which was purified by column chromatography to give **29-4** (350 mg). +ESI-MS: m/z 356.0[M + H]⁺.

[1242] Compound **2901** was prepared using **29-4** and by following a synthetic route, which closely follows that described for preparation of compound **2900**. +ESI-MS: m/z 489.9[M + H]⁺.

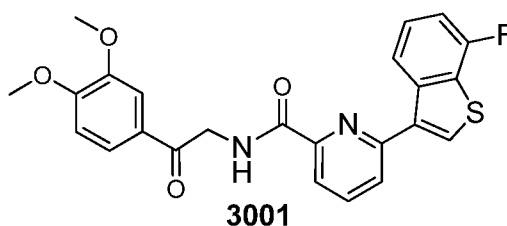
EXAMPLE 30-1
Preparation of Compound 3000



[1243] Compound **30-1** (1.08 g, 5 mmol), the dioxaborolane (1.526 g, 5.5 mmol), K_2CO_3 (1.03 g) and $Pd(dppf)Cl_2$ (366 mg, 0.5 mmol) were dissolved in dioxane (10 mL) and H_2O (5 mL), and the mixture stirred under argon at $90^\circ C$ for 10 h. The solvent was removed to give the crude product. The residue was purified by column on silica gel (PE:EA=10:1) to give **30-2** (440 mg, 30.6%). +ESI-MS: m/z 288.0 $[M+H]^+$.

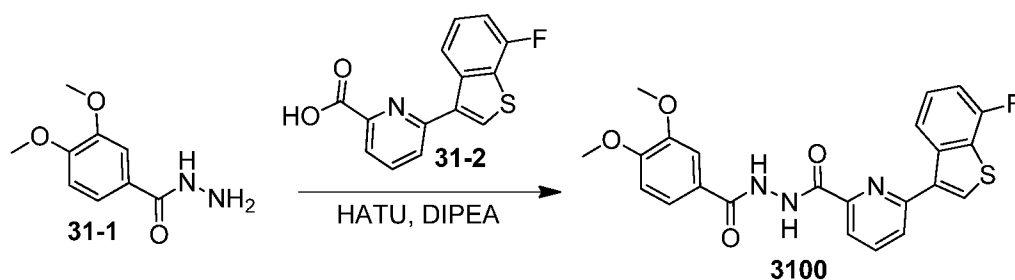
[1244] To a solution of **30-2** (220 mg, 0.8 mmol) in MeOH (3 mL) and H_2O (1 mL) was added KOH (67 mg, 1.2 mmol). The mixture was refluxed for 1 h., and concentrated at low pressure. The residue was dissolved in H_2O and EtOAc, and acidified to pH (3-4) by adding HCl solution (2M, 0.5 mL). The organic phase was concentrated at low pressure to give **30-3** (200 mg, 91.5%). +ESI-MS: m/z 274.0 $[M+H]^+$.

[1245] To a solution of **30-3** (100 mg, 0.37 mmol), 2-amino-1-(3,4-dimethoxyphenyl)ethanol (108 mg, 0.55 mmol), DIPEA (0.2 mL) in DMF (1.5 mL) was added HATU (209 mg, 0.55 mmol). The mixture was stirred at $25^\circ C$ for 10 h. The mixture was purified by prep-TLC (PE:EA=1:1) to give compound **3000** (40 mg, 24%). +ESI-MS: m/z 474.9 $[M+Na]^+$.



[1246] To a solution of Compound **3000** (40 mg, 0.09 mmol) in DCM (4 mL) was added DMP (115 mg, 0.27 mmol). The mixture was stirred at 25°C for 1 h. The mixture was washed with saturated Na₂S₂O₃ solution and saturated NaHCO₃. The organic phase was washed with brine, dried over Na₂SO₄, and concentrated at low pressure. The residue was purified by column on silica gel (PE:EA=1:1) to give compound **3001** (15 mg, 30%). +ESI-MS:m/z 450.9 [M + H]⁺.

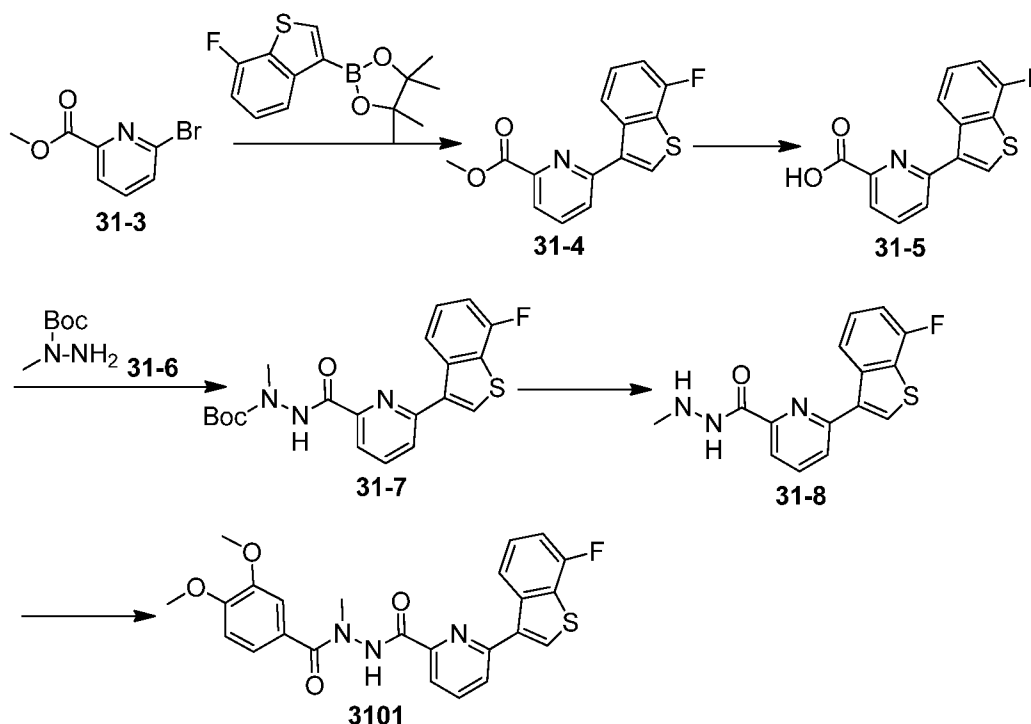
EXAMPLE 31-1
Preparation of Compound 3100



[1247] Compound **31-1** was prepared according to the procedure in Murty et al., *Letters in Drug Design & Discovery* (2012) 9(3):276-281, which hereby is incorporated by reference for the limited purpose of preparing **31-1**.

[1248] To a solution of **31-1** (100 mg, 0.36 mmol), HATU (200 mg, 0.52 mmol) and DIPEA (140 mg, 1.08 mmol) in anhydrous DCM (3 mL) was added **31-2** (76 mg, 0.36 mmol) at 25°C. The solution was stirred for 8 h at this temperature and then diluted with 1.0 N aqueous NaHCO₃ solution (30 mL x 2), and extracted with EA (30 mL x 2). The combined organic layers were washed by brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give compound **3100** (8 mg) as a white solid. +ESI-MS: :m/z 452.0[M + H]⁺.

EXAMPLE 31-2
Preparation of Compound 3101



[1249] To a solution of **31-3** (1.0 g, 4.6 mmol) and the dioxaborolane (1.6 g, 5.7 mmol) in dioxane (10 mL) were added Pd (PPh₃)₂Cl₂ (50 mg, 0.06 mmol) and a freshly prepared K₂CO₃ solution (0.95 g in 2 mL of water). The system was degassed and then charged with nitrogen 3 times. The mixture was stirred under nitrogen at 70°C in an oil bath for 2 h. The solution was cooled to rt, diluted with EA and separated from the water layer. The EA solution was washed by brine, dried over Na₂SO₄ and concentrated. The residue was chromatographed on silica gel to give **31-4** (0.9 g) as a white solid. +ESI-MS: m/z = 287.7 [M + H]⁺.

[1250] To a solution of **31-4** (0.9 g, 3.1 mmol) in MeOH (5 mL) was added NaOH (5 mL, 2.5M NaOH in H₂O). The solution was stirred at 60°C for 1 h. After the solvent evaporated to a small volume, H₂O (50 mL) was added and the solution was extracted with DCM (2 x 20 mL). The aqueous phase was cooled on an ice-water bath. The pH was adjusted to 7 by adding 25% v/v HCl. The precipitate was filtered and dried under vacuum to give **31-5** (700 mg) as a white solid. +ESI-MS: m/z = 273.8 [M + H]⁺.

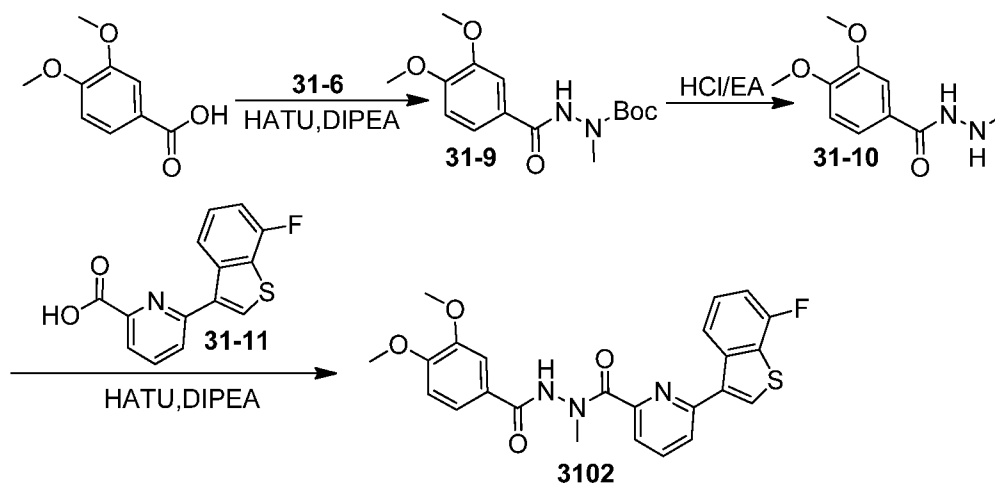
[1251] To a solution of **31-5** (600 mg, 2.2 mmol), HATU (1.1 g, 2.9 mmol) and DIPEA (700 mg, 5.4 mmol) in anhydrous DCM (5 mL) was added **31-6** (400 mg, 2.7 mmol)

at 25°C. The solution was stirred for 10 h at this temperature and then diluted with 1.0 N aqueous NaHCO₃ solution (40 mL x 2), and extracted with EA (50 mL x 2). The combined organic layers were washed by brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by chromatograph on a silica gel column to give **31-7** (800 mg) as a white solid. +ESI-MS: $m/z = 401.9$ [M + H]⁺.

[1252] To a solution of **31-7** (800 mg, 2.0 mmol) in EtOAc (10 mL) was added HCl/EA (8 mL) at 0°C. The solution was stirred at 25°C for 1 h with TLC monitoring. A precipitate formed and was collected by filtration. The solid was washed with EA to give **31-8** (800 mg) as a white solid. +ESI-MS: $m/z = 302.0$ [M + H]⁺.

[1253] To a solution of 3,4-dimethoxybenzoic acid (60 mg, 0.33 mmol), HATU (180 mg, 0.47 mmol) and DIPEA (120 mg, 0.95 mmol) in anhydrous DCM (3 mL) was added **31-8** (100 mg, 0.33 mmol) at 25°C. The solution was stirred for 8 h. at this temperature and then diluted with 1.0 N aqueous NaHCO₃ solution (50 mL x 2), and extracted with EA (50 mL x 2). The combined organic layers were washed by brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give compound **3101** (40 mg) as a white solid. +ESI-MS: $m/z = 466.1$ [M + H]⁺.

EXAMPLE 31-3 Preparation of Compound 3102



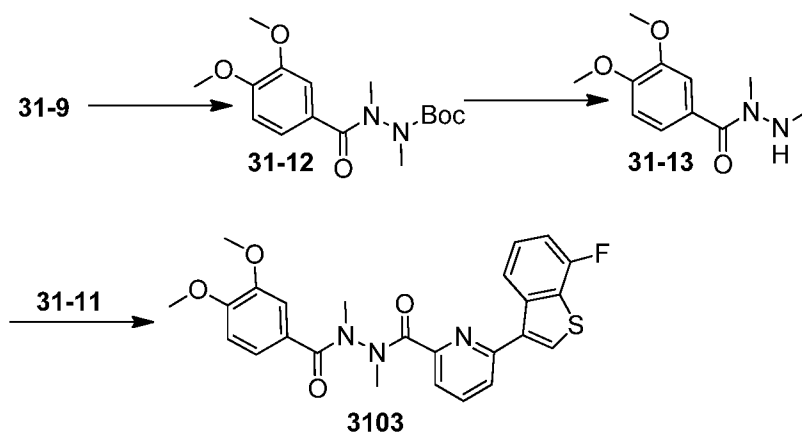
[1254] To a solution of 3,4-dimethoxybenzoic acid (1.82 g, 10 mmol), HATU (4.5 g, 11.8 mmol) and DIPEA (3.8 g, 29.4 mmol) in anhydrous DCM (10 mL) was added **31-6** (1.47 mg, 10.0 mmol) at 25°C. The solution was stirred for 10 h at this temperature and

then diluted with 1.0 N aqueous NaHCO_3 solution (80 mL x 2), extracted with EA (80 mL x 2). The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified on a silica gel column to give **31-9** (1.8 g) as a white solid. +ESI-MS: $m/z = 311.1$ $[\text{M} + \text{H}]^+$

[1255] To a solution of **31-9** (800 mg, 2.6 mmol) in EA (10 mL) was added HCl/EA (8 mL) at 0°C . The solution was stirred at 25°C for 1 h with TLC monitoring. A precipitate formed and was collected by filtration. The solid was washed with EA to give **31-10** (500 mg) as a white solid. +ESI-MS: $m/z = 211.1$ $[\text{M} + \text{H}]^+$

[1256] To a solution of **31-11** (130 mg, 0.48 mmol), HATU (250 mg, 0.65 mmol) and DIPEA (200 mg, 1.55 mmol) in anhydrous DCM (3 mL) was added **31-10** (100 mg, 0.48 mmol) at 25°C . The solution was stirred for 8 h at this temperature and then diluted with 1.0 N aqueous NaHCO_3 solution (30 mL x 2), and extracted with EA (30 mL x 2). The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified on a silica gel column to give compound **3102** (60 mg) as a white solid. +ESI-MS: $m/z = 466.1$ $[\text{M} + \text{H}]^+$.

EXAMPLE 31-4
Preparation of Compound 3103

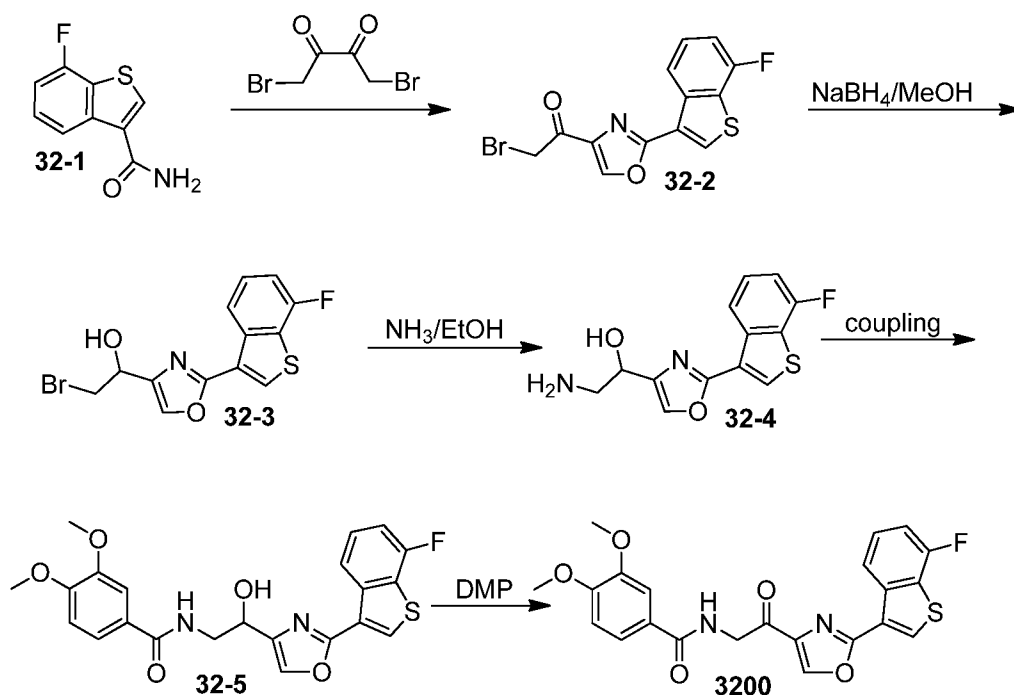


[1257] A mixture of **31-9** (1.0 g, 3.2 mmol), K_2CO_3 (1.7 g, 12 mmol) and CH_3I (2.3 g, 16 mmol) in DMF in a seal tube was stirred at 70°C for 8 h. The mixture was diluted with EA. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column to give **31-12** (800 mg) as a white solid. +ESI-MS: $m/z = 325.1$ $[\text{M} + \text{H}]^+$.

[1258] To a solution of **31-12** (800 mg, 2.4 mmol) in EA (10 mL) was added HCl/EA (8 mL) at 0°C. The solution was stirred at 25°C for 1 h with TLC monitoring. A precipitate formed and was collected by filtration. The solid was washed with EA to give **31-13** (400 mg) as a white solid. +ESI-MS: $m/z = 225.1[M + H]^+$

[1259] To a solution of **31-11** (100 mg, 0.37 mmol), HATU (250 mg, 0.65 mmol) and DIPEA (200 mg, 1.55 mmol) in anhydrous DCM (3 mL) was added **31-13** (80 mg, 0.38 mmol) at 25°C. The solution was stirred for 8 h at this temperature and then diluted with 1.0 N aqueous NaHCO₃ solution (30 mL x 2), and extracted with EA (30 mL x 2). The combined organic layers were washed by brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified on a silica gel column to give compound **3103** (120 mg) as a white solid. +ESI-MS: $m/z = 480.1[M + H]^+$.

EXAMPLE 32-1
Preparation of Compound 3200



[1260] To a solution of **32-1** (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 **32-2** (270 mg, 80%). +ESI-MS: m/z 339. 9 $[M + H]^+$.

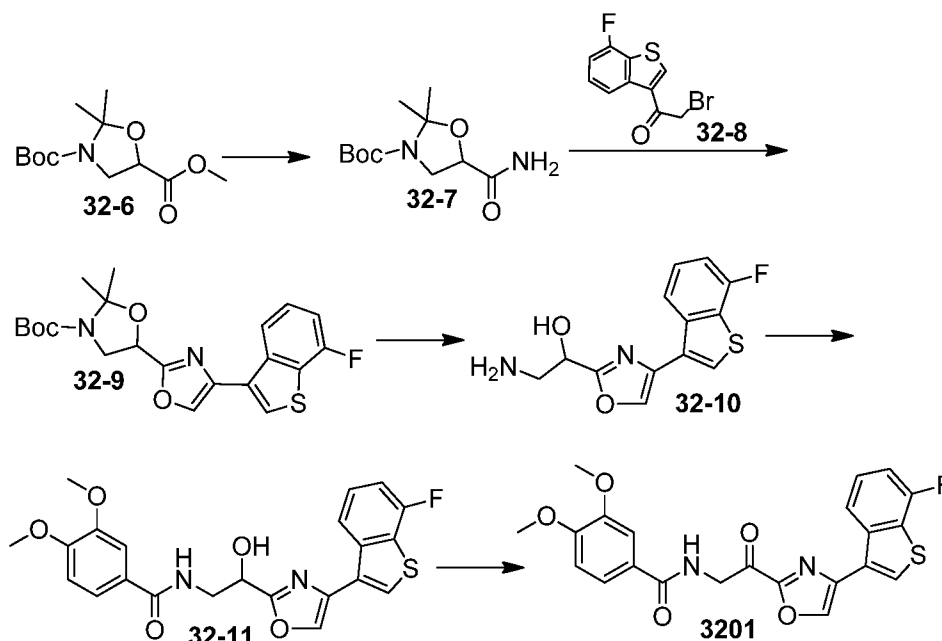
[1261] To a solution of **32-2** (340 mg, 1.0 mmol) in MeOH (10mL) was added NaBH₄ (380 mg, 10 mmol) in portions until the starting materials was consumed. The volatiles were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (PE: EtOAc=2:1) to give **32-3** (340 mg, 99%). +ESI-MS: m/z 341. 9 [M +H]⁺.

[1262] Compound **32-3** was dissolved in EtOH/NH₄OH(10 mL/10 mL). After sealing in autoclave, the mixture was stirred at 90°C for 10 h., and then extracted with EtOAc. The organic phase was dried over anhydrous Na₂SO₄, and concentrated at low pressure to give **32-4**. +ESI-MS: m/z 279.0 [M +H]⁺.

[1263] The carboxyl acid (90 mg, 0.5 mmol), amine (140 mg, 0.5 mmol) and triethylamine (1 mmol) are dissolved in DMF (15 mL), and HATU (380 mg, 1 mmol) was added to the solution. After 15-30 mins, saturated NaCl solution (100 mL) was added. The solution was extracted with EtOAc (3 x 10 mL). The combined organics were washed with 2N HCl and 5% NaHCO₃. The organic phase were dried over MgSO₄, and concentrated at low pressure to give the crude product. The crude was purified by silica gel column chromatography with EtOAc/PE (1/1) as the elute to give **32-5** (100 mg, 48 %). +ESI-MS: m/z 442. 9 [M +H]⁺.

[1264] To a solution of **32-5** (88 mg, 0.2 mmol) in CH₂Cl₂ (10 mL) was added DMP (170 mg, 0.4 mmol), and the mixture was stirred at rt until the starting material was consumed. After work-up, the solution was concentrated to give the crude product. The residue was purified by silica gel column chromatography (PE/EA) to give compound **3200** (62 mg, 70%). +ESI-MS: m/z 441. 0 [M +H]⁺.

EXAMPLE 32-2
Preparation of Compound 3201



[1265] A solution of **32-6** (2.59 g, 0.01 mol) in NH_3/MeOH (20 mL) was stirred at rt for 30 mins. The solvent was removed by rotary evaporator. The residue, **32-7**, was used in next step.

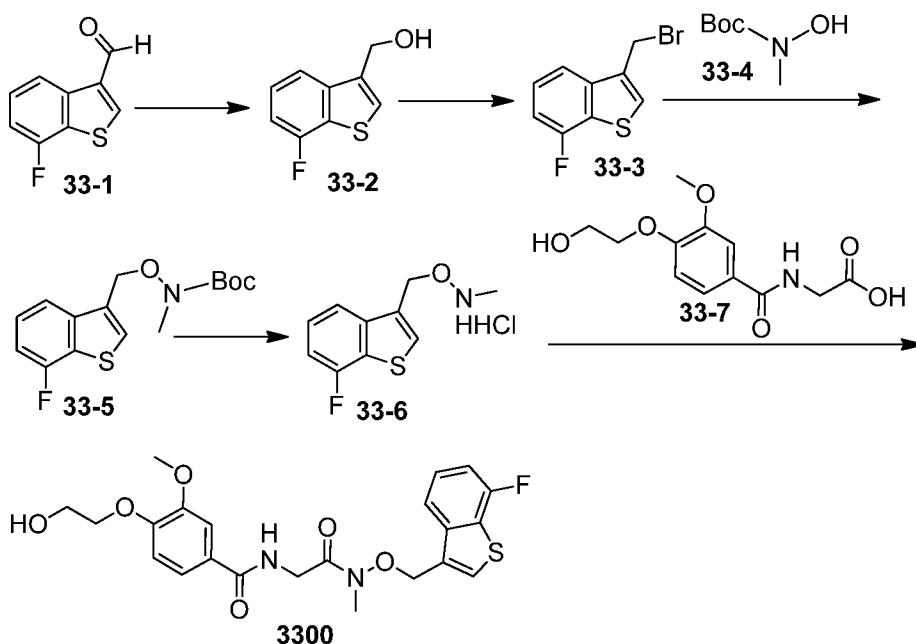
[1266] A mixture of **32-7** (2.44 g, 0.01 mol) **32-8** (2.73 g, 0.01 mol) and AgSbF_6 (5.14 g, 0.015 mol) in DME (20 mL) was stirred for 2 h at 120°C under microwave irradiation. The mixture was filtrated. The filtrate was concentrated by rotary evaporator to give crude **32-9** (5 g), which was used in next step without further purification.

[1267] To a solution of **32-9** (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 **32-10** (250 mg). ESI-MS: m/z 278.8 $[\text{M}+\text{H}]^+$.

[1268] To a solution of **32-10** (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 min. 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 chromatograph (PE:EA=1:1) to give **32-11** (158 mg, 45%). ESI-MS: m/z 442.9 $[\text{M}+\text{H}]^+$.

[1269] To a solution of **32-11** (158 mg, 0.35 mmol) in dry DCM (5 mL) was added DMP (300 mg, 0.7 mmol) at 0°C and the mixture was stirred for 1 h (monitored by TLC). The product was purified by prep-HPLC to give compound **3201** (15 mg, yield 10%). +ESI-MS: m/z 440.9 $[M+H]^+$.

EXAMPLE 33-1
Preparation of Compound 3300



[1270] To a solution of **33-1** (2 g, 11 mmol) in THF (20 mL) and MeOH (2 mL) was added NaBH_4 (386 mg, 11.2 mmol) at 0°C, and the mixture was stirred for 30 mins (monitored by TLC). The reaction was quenched by addition of H_2O and extracted by EA. The combined organic layers were washed by brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column to give **33-2** (1.5 g, 75%).

[1271] To a solution of **33-2** (1.09 g, 6 mmol) in DCM (10 mL) was added PBr_3 (2 mL), and the mixture was stirred for 30 mins at rt. The solution was quenched with water and extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column to give **33-3** (0.5 g, 34%).

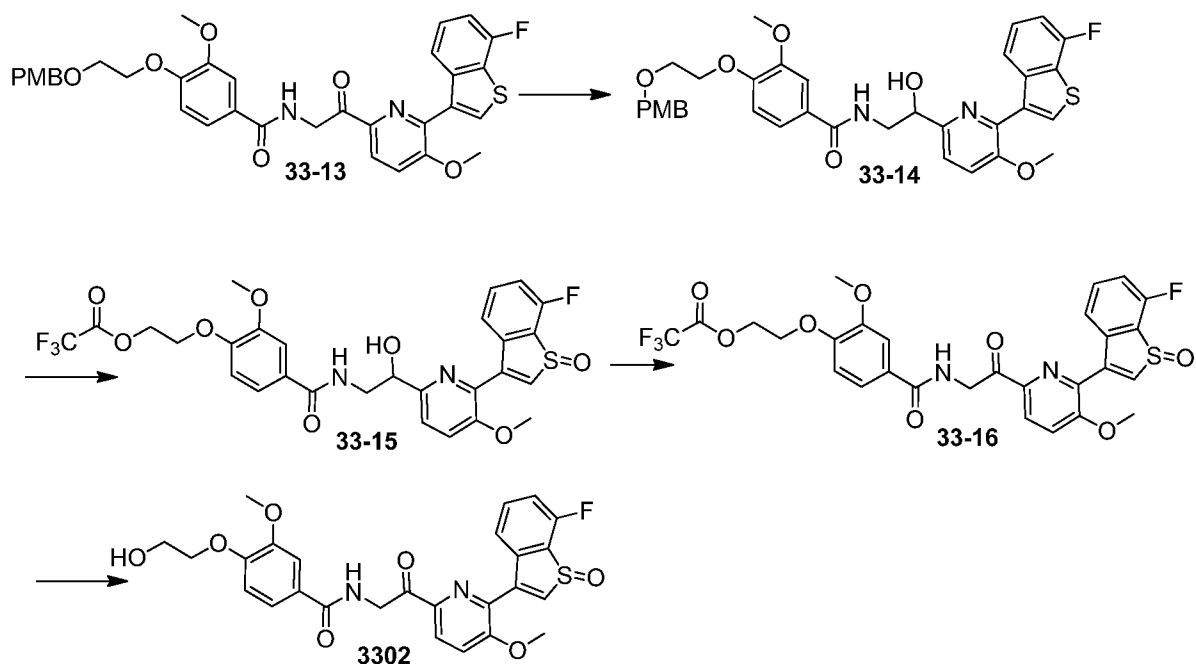
[1272] To a solution of **33-3** (490 mg, 2 mmol) in THF (5 mL) was added NaH (96 mg, 4 mmol) at 0°C. The solution was stirred for 30 mins at 0°C. Compound **33-4** (294 mg, 2 mmol) (prepared according to Hunt et al., *Org. Lett.* (2009) 11(22):5210-5213, which hereby is incorporated by reference for the limited purpose of preparing **33-4**) was added.

The solution was stirred for 30 mins at rt. The mixture was washed with H₂O and diluted with EA. The solution was washed by brine, dried over Na₂SO₄ and concentrated to give crude **33-5** (400 mg, 64.0%).

[1273] A solution of **33-5** (311 mg, 1 mmol) in EA (2 mL) was added EA/HCl (2 mL). The solution was stirred for 30 mins. The solid was collected to give **33-6** (247 mg, 100%)

[1274] To a solution of **33-7** (100 mg, 0.37 mmol), HATU (172 mg, 0.45 mmol) and DIPEA (117 mg, 0.909 mmol) in anhydrous DMF (1 mL) was added **33-6** (100 mg 0.404 mmol) at 25°C. The solution was stirred for 10 h at this temperature, diluted with 1.0 N aqueous NaHCO₃ solution (40 mL x 2), and extracted with EA (20 mL x 2). The combined organic layers were washed by brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified on a silica gel column to give compound **3300** (20 mg, 11.7%). +ESI-MS: m/z 463.1 [M+H]⁺.

EXAMPLE 33-2 **Preparation of Compound 3302**



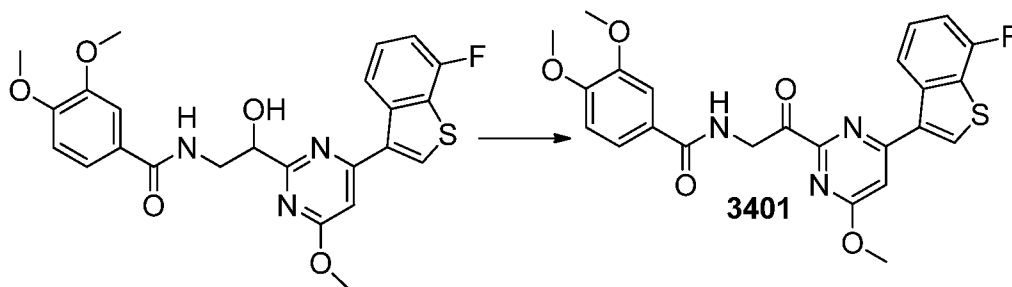
[1275] To a solution of **33-13** (190 mg, 0.30mmol) in THF (5 mL) was added NaBH₄ (20 mg, 0.6 mmol) at rt. MeOH (1mL) was added, and the mixture was stirred at

20°C for 1 h. The residue was purified by column chromatography on silica gel (PE) to provide **33-14** (190 mg, 99 %).

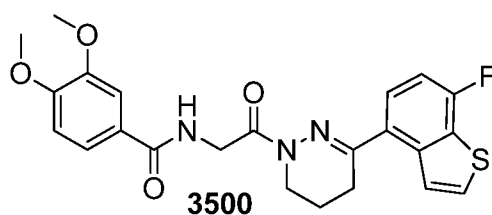
[1276] To a solution of **33-14** (190 mg, 0.3 mmol) in DCM (3 mL) was added TFA (0.5 mL) and H₂O₂ (0.2 mL, 30%, 2eq), and the mixture was stirred for 30 mins. The mixture was neutralized with a saturated NaHCO₃ solution, and extracted with DCM (10 mL x 3). The solution was concentrated to give crude **33-15** (200 mg), which was used in the next step without further purification. +ESI-MS: m/z 625.0 [M + H]⁺.

[1277] To a solution of **33-15** (200 mg, 0.3 mmol) in CH₂Cl₂ (5 mL) was added DMP (170 mg, 0.4 mmol), and the mixture was stirred at rt until the starting material was consumed. After work up, **33-16** was obtained and used in the next step without further purification.

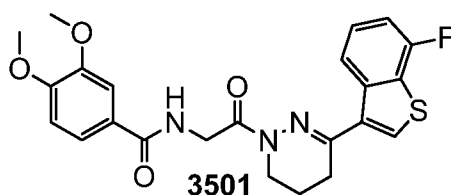
[1278] To a solution of **33-16** (200 mg, 0.3 mmol) in MeOH (10 mL) was added one drop of concentrated HCl (1 mL). The mixture was stirred at rt until the starting material was consumed. Work up and concentration of the residue provided compound **3302**. Purification by prep-HPLC gave compound **3302** (13 mg, 7%). +ESI-MS: m/z 526.9 [M + H]⁺.



[1279] To a stirred solution of N-(2-(4-(7-fluorobenzo[b]thiophen-3-yl)-6-methoxypyrimidin-2-yl)-2-hydroxyethyl)-3,4-dimethoxybenzamide (96 mg, 0.2 mmol) in DCM (10 mL) was added DMP (170 mg, 0.4 mmol). The mixture was stirred at rt until the starting material was consumed. The mixture was diluted with dichloromethane (20 mL), and washed with saturated Na₂S₂O₃ solution and NaHCO₃ solution. The organic phase was dried over anhydrous MgSO₄, and concentrated to give the crude product. The residue was purified by silica gel column chromatography (PE/EA) to give compound **3401** (74 mg, 80%). +ESI-MS: m/z 482.9 [M + H]⁺.

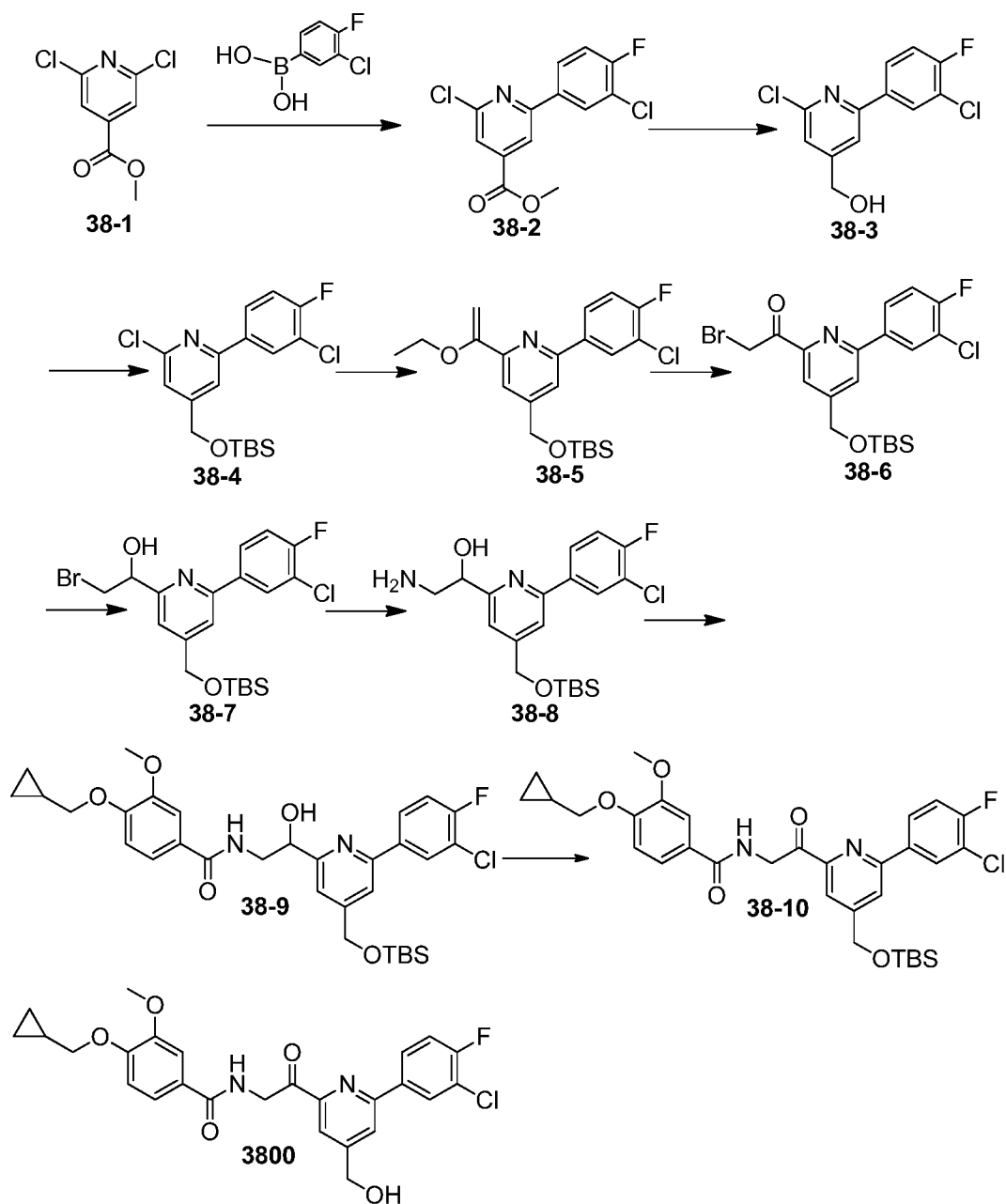


[1280] Compound **3500** was prepared using methyl 3,4-dimethoxybenzoic acid and 2,3-difluorobenzaldehyde, and by following a synthetic route, which closely follows that described for preparation of compound **200**. Compound **3500** was obtained as a white solid (168.9mg, 35.2%). +ESI-MS:m/z 456.1[M + H]⁺.



[1281] Compound **3501** was prepared using methyl methyl 3,4-dimethoxybenzoic acid and 2,3-difluorobenzaldehyde, and by following a synthetic route, which closely follows that described for preparation of compound **200**. Compound **3501** was obtained as a white solid (76.4 mg, 14.9%). +ESI-MS:m/z 456.0[M + H]⁺.

EXAMPLE 34-1
Preparation of Compound 3800



[1282] To a solution of **38-1** (3 g, 14 mmol) and the boronic acid (2.5 g, 14 mmol) in dioxane/H₂O (30 mL/5 mL) was added Pd(dppf)Cl₂ (1.02 g, 1.4 mmol) and Cs₂CO₃ (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 rt, diluted with EA and separated from the water layer. The EA solution was washed by

brine, dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give **38-2** (2 g, 47.9%).

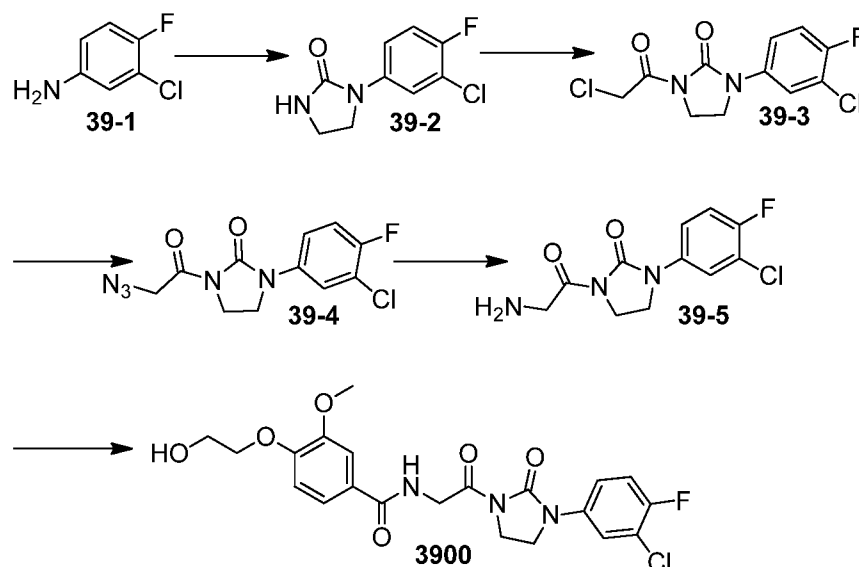
[1283] To a solution of **38-2** (2 g, 6.7 mmol) in MeOH/DCM (20 mL/20 mL) was added NaBH₄ (510 mg, 13.4 mmol) slowly at 0°C. The solution was stirred for 10 mins and heated to 50°C and stirred for 2 h. The solution was quenched with H₂O and extracted with EA. The solution was concentrated to give crude **38-3** (1.81 g, 100 %).

[1284] To a solution of **38-3** (1.81 g, 6.7 mmol) in DMF was added imidazole (1.36 g, 1.34 mmol) at rt. 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 **38-4** (1.8 g, 70.0%). ESI-LCMS: m/z = 385.9 [M + H]⁺.

[1285] Compound **38-10** was prepared using **38-4**, and by following a synthetic route, which closely follows that described for preparation of **1200**. ¹H-NMR (400 MHz, CDCl₃), 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).

[1286] To a solution of **38-10** (100 mg, 0.163 mmol) in dioxane (2 mL) was added concentrated HCl (2 mL) at rt and the mixture was stirred for 30 mins. The solution was quenched by aqueous NaHCO₃ solution and extracted by EA. The combined organic layers were washed by brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC(FA) to give compound **3800** (30 mg, 37.0%) as a white solid. +ESI-MS: m/z 498.9 [M + H]⁺.

EXAMPLE 35-1
Preparation of Compound 3900

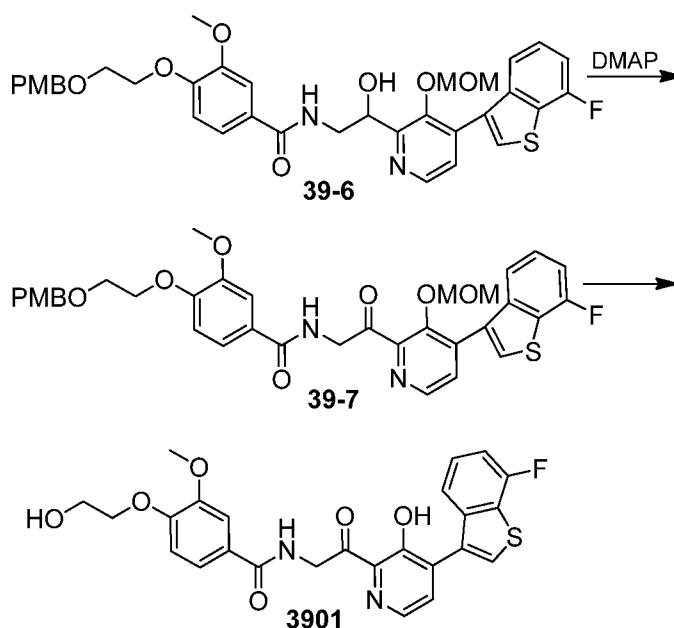


[1287] A round bottom flask was charged with **39-1** (1.45 g, 10.0 mmol) in THF (20 mL). 1-chloro-2-isocyanatoethane (1.2 g, 11 mmol) was added dropwise. The mixture was stirred at rt for 30 mins. NaH (400 mg, 10 mmol, 60% in mineral oil) was added. The mixture was stirred at 50°C for 3 h. The reaction was quenched with MeOH, and diluted with EA (50 mL). The solution was washed with brine. The organic solution was dried over anhydrous MgSO₄, and concentrated at low pressure. The residue was purified by chromatograph to give **39-2** (1.04 g, 50%). +ESI-MS: m/z 214.9 [M + H]⁺

[1288] A round bottom flask was charged with **39-2** (214 mg, 1.0 mmol), 2-chloroacetic anhydride (340 mg, 2eq) in PhMe (20 mL). The mixture was stirred at 120°C for 3 h. The solvent was removed in vacuum. The residue was purified by column on silica gel (PE:EA=5:1) to give **39-3** (260 mg, 90%). +ESI-MS: m/z 291.1 [M + H]⁺.

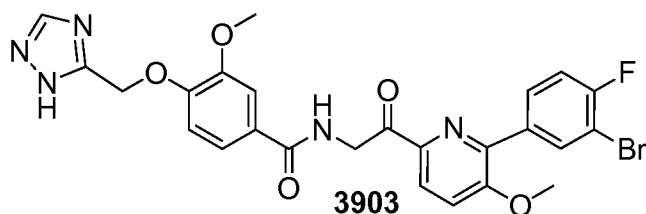
[1289] Compound **3900** was prepared using **39-3**, and by following a synthetic route, which closely follows that described for preparation of compound **2800**. +ESI-MS: m/z 465.8 [M + H]⁺.

EXAMPLE 35-2
Preparation of Compound 3901

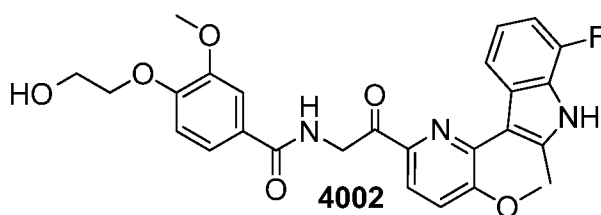


[1290] Compound **39-7** was prepared using 2-chloro-4-iodo-3-(methoxymethoxy) pyridine, and by following a synthetic route, which closely follows that described for preparation of **1200**.

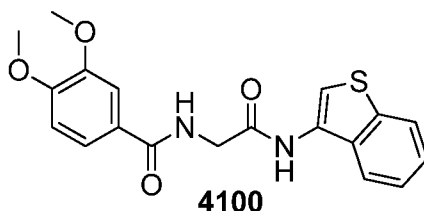
[1291] To a solution of crude **39-7** (150mg, 0.226 mmol) in DCM (20 mL) was added TFA (2 mL). The mixture was stirred at rt for 30 mins. The solution was washed with water and extracted with EA. The organic layer was dried over anhydrous MgSO_4 , and concentrated at low pressure. The residue was purified by prep-HPLC to generate compound **3901** (29 mg, 8.7 %). +ESI-MS: m/z 496.9 $[\text{M} + \text{H}]^+$.



[1292] Compound **3903** was prepared using 2-amino-1-(6-(3-bromo-4-fluorophenyl)-5-methoxypyridin-2-yl) ethanol, and by following a synthetic route, which closely follows that described for preparation of compound **1310**. +ESI-MS: m/z 569.9 $[\text{M} + \text{H}]^+$.

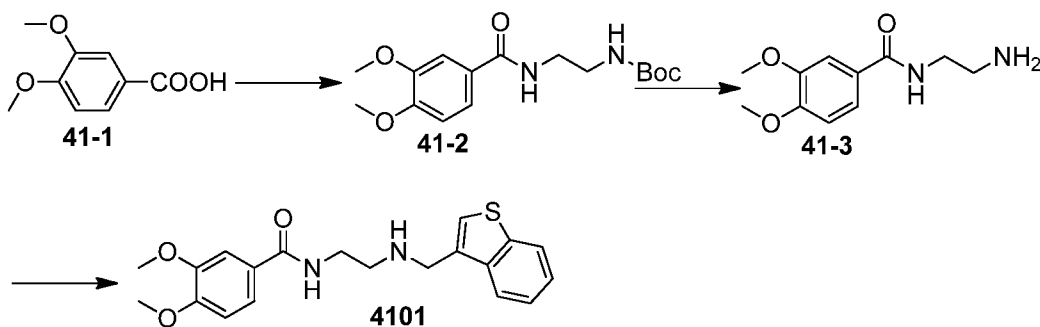


[1293] Compound **4002** was prepared using N-(2-(6-bromo-5-methoxypyridin-2-yl)-2-oxoethyl)-3-methoxy-4-(2-((4-methoxybenzyl)oxy)ethoxy)benzamide and 7-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole, and by following a synthetic route, which closely follows that described for preparation of compound **1300**. +ESI-MS:m/z 508.3 [M + H]⁺.



[1294] Compound **4100** was prepared using 3,4-dimethoxybenzoic acid and benzo[b]thiophen-3-amine, and by following a synthetic route, which closely follows that described for preparation of compound **200**. Compound **4100** was obtained as a white solid. ESI-LCMS: m/z = 371.0 [M + H]⁺.

EXAMPLE 36-1 **Preparation of Compound 4101**

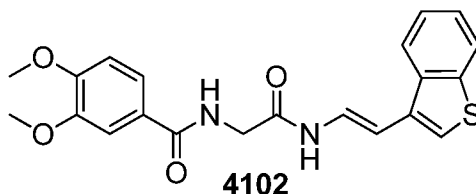


[1295] To a solution of **41-1** (3.0 g, 16.5 mmol) in DCM (50 mL) was added HATU (9.4 g, 24.7 mmol) and DIPEA (8.4 g, 65.0 mmol), and the mixture was stirred at rt for 30 mins. The mixture was treated with tert-butyl (2-aminoethyl)carbamate (4.0 g, 24.7 mmol). The mixture was then stirred at rt for 15 h. The mixture was washed with water and the organic layer was separated. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by column chromatograph on silica gel

(PE:EA=50:1 to 10:1) to afford **41-2** as a white solid (3.2g, 60.3%). +ESI-LCMS: $m/z = 324.9 [M + H]^+$.

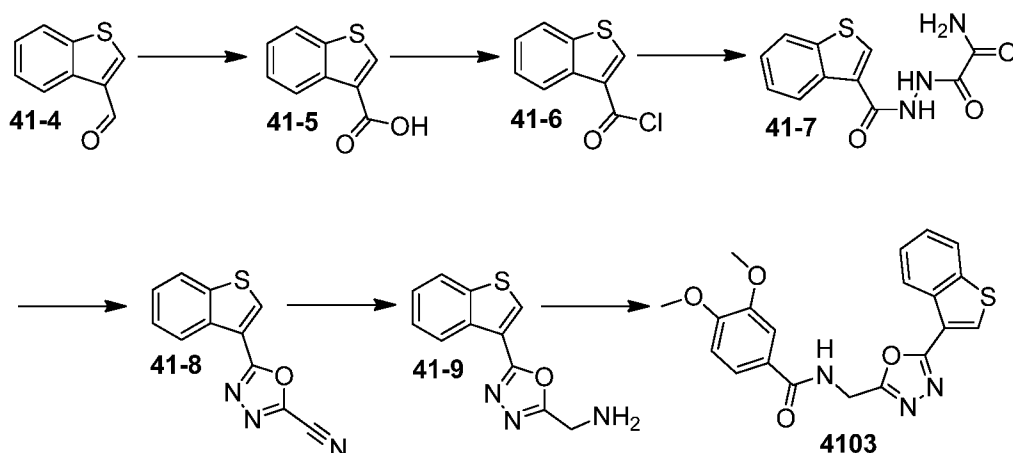
[1296] Compound **41-2** (3.2 g, 9.7 mmol) was dissolved in HCl/EtOAc (6.0 M, 60 mL) and stirred at rt for 15 h. The mixture was concentrated to dryness. The residue was dissolved in water, basified with saturated Na_2CO_3 , extracted with EA and purified by column chromatograph on silica gel (eluent: PE:EA=20:1 to 2:1) to give **41-3** as a white solid (1.9g, 87%). +ESI-LCMS: $m/z = 224.9 [M + H]^+$.

[1297] To a solution of **41-3** (450 mg, 2.00 mmol) and benzo[b]thiophene-3-carbaldehyde (350 mg, 1.85 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (10 mL) was added NaBH_4 (150mg, 3.95mmol), and the mixture was stirred at 50°C for 15 h. The reaction was quenched with water (10 mL). The organic layer was separated, washed with saturated NH_4Cl , and dried over Na_2SO_4 . The organic solvent was concentrated at low pressure. The residue was finally purified by column chromatograph on silica gel (eluent: PE:EA=20:1 to 1:1) to afford compound **4101** as a white solid (236 mg, 29.8%). ESI-LCMS: $m/z = 371.0 [M + H]^+$.



[1298] Compound **4102** (30 mg, 2.6%) was prepared using 3,4-dimethoxybenzoic acid and 1-(benzo[b]thiophen-3-yl)ethanone, and by following a synthetic route, which closely follows that described for preparation of **200**. Compound **4102** was obtained as a white solid. +ESI-MS: $m/z 436.9 [M + \text{MeCN}]^+$.

EXAMPLE 36-2
Preparation of Compound 4103



[1299] To a solution of **41-4** (6 g, 37 mmol) in MeOH (25 mL) and H₂O (250 mL) was added KMnO₄ (23 g, 145 mmol). The mixture was stirred at 80°C for 13 h. The mixture was filtered, and the filtrate was concentrated, and acidified to pH = 3.0 with 2N HCl solution. The precipitate was collected by filtration and washed with H₂O to give **41-5**. ESI-LCMS: m/z = 178.9 [M + H]⁺.

[1300] A mixture of **41-5** (1.5 g, 8.4 mmol) and SOCl₂ (5 g, 42 mmol) was refluxed for 4 h. Excess SOCl₂ was removed under reduced pressure and the residue was concentrated to give crude **41-6**, which was used for next step without purification.

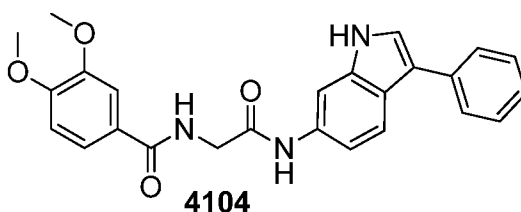
[1301] To a solution of **41-6** (1.5 g, 7.6 mmol) in dioxane (3 mL) was added a mixture 2-hydrazinyl-2-oxoacetamide (0.79 g, 7.6 mmol) and NaHCO₃ (0.64 g, 7.6 mmol) in dioxane (30 mL) dropwise. The mixture was refluxed for 4 h, and filtered hot. The filtrate was concentrated in vacuum to afford crude **41-7**, which was used in next step without purification. ESI-LCMS: m/z = 263.9 [M + H]⁺.

[1302] A suspension of **41-7** in POCl₃ (20 mL) was heated to 100°C for 3 h. POCl₃ was evaporated in vacuum. The mixture was diluted with EA (50 mL), and neutralized with an ice-cold saturated NaHCO₃ solution. The organic layer was dried over sodium sulfate and concentrated to give crude **41-8**, which was used in next step without purification. ESI-LCMS: m/z = 227.8 [M + H]⁺.

[1303] A mixture of **41-8** (220 mg, 0.97 mmol), concentrated HCl (3 mL) and Pd/C (100 mg) in EtOH (15 mL) was stirred under hydrogen (15 psi) for 13 h. The mixture was filtered over a pad of celite and the filtrate was concentrated in vacuum. The residue

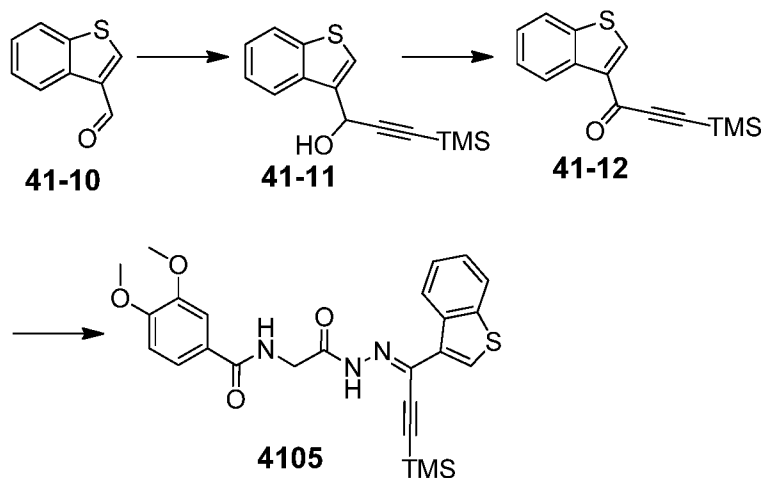
was diluted by DCM and water. The aqueous phase was basified by aq. NaOH (5 N), and extracted with DCM. The combined organic phase was dried over sodium sulfate, and concentrated at low pressure to give crude **41-9**, which was used in next step without purification.

[1304] To a solution of 3,4-dimethoxybenzoic acid (24 mg, 0.13 mmol), HATU (60 mg, 0.16 mmol) and DIPEA (45 mg, 0.35 mmol) in anhydrous DCM (3 mL) was added **41-9** (30 mg, 0.13 mmol). The solution was stirred for 10 h at rt and then diluted with 1.0 N aqueous NaHCO₃ solution. The mixture was extracted with DCM. The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to give compound **4103** (15 mg, 30 %). ESI-LCMS: m/z = 396.0 [M + H]⁺.



[1305] Compound **4104** (4 mg, 2.1%) was prepared using 3,4-dimethoxybenzoic acid, (3-nitro-phenyl)-hydrazine and phenyl-acetaldehyde, and by following a synthetic route, which closely follows that described for preparation of compound **200**. Compound **4104** was obtained as a white solid. +ESI-MS:m/z 430.2[M + H]⁺.

EXAMPLE 36-3 **Preparation of Compound 4105**

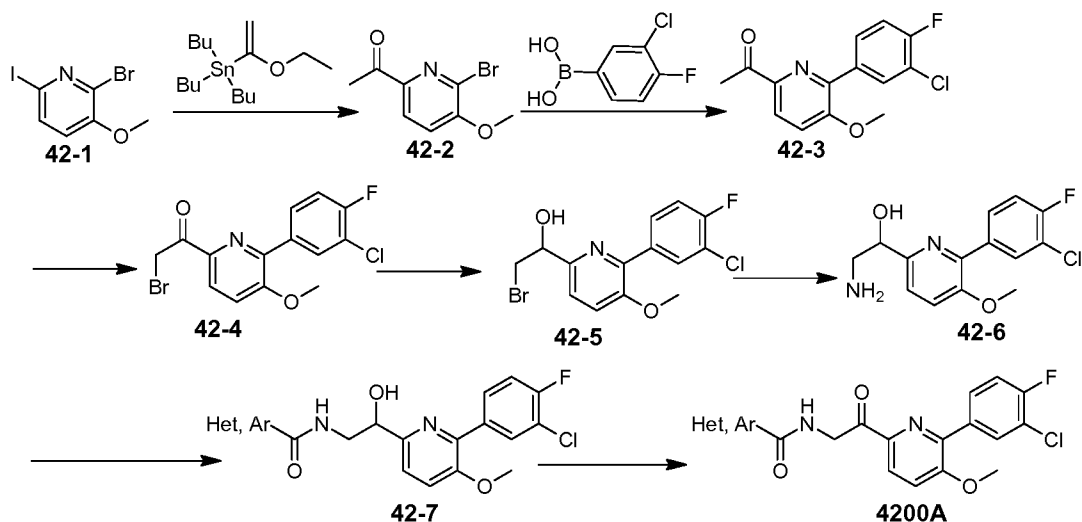


[1306] To a stirred solution of ethynyltrimethylsilane (667 mg, 6.79 eq) in DMF (5 mL) was added sodium hydride (296 mg, 7.4 mmol), and the mixture was stirred at rt over 1 h. Benzo[b]thiophene-3-carbaldehyde (**41-10**, 1.0g, 6.17 mmol) was added portion-wise. The mixture was stirred at rt for more than 2 h., and then quenched with water. The mixture was extracted with EA, and concentrated at low pressure. The residue was purified by silica gel (PE/EA=5/1) to give **41-11** (600 mg, 37%). ¹H-NMR (CDCl₃, 400MHz), δ = 7.87-7.3 (m, 3H), 7.42-7.34 (m, 2H), 4.93 (s, 1H), 0.22 (s, 9H).

[1307] To a solution of **41-11** (0.6 g, 2.3 mmol) in DCM was added PCC (993 mg, 4.6 mmol), and the mixture was stirred at rt for more than 4 h. The reaction was quenched with saturated NH₄Cl solution. The solution was extracted with DCM, and concentrated at low pressure. The residue was purified by silica gel (PE/EA=8/1) to give **41-12** (200 mg, 34%). ¹H-NMR (CDCl₃, 400MHz), δ = 8.76-7.74 (d, J=8.0 Hz, 1H), 8.65 (s, 1H), 7.88-7.86 (d, J=8.0 Hz, 1H), 7.53-7.49 (t, J=3.6 Hz, 1H), 7.46-7.42 (t, J=3.6 Hz, 1H), 0.32 (s, 9H).

[1308] To a solution of **41-12** (0.1g, 0.387 mmol) in EtOH (5 mL) was added N-(2-hydrazinyl-2-oxoethyl)-3,4-dimethoxybenzamide (98 mg, 0.387 mmol), and the mixture was stirred at rt for more than 6 h. The mixture was then slowly heated to 70°C for 2 h. The mixture was concentrated at low pressure. The residue was purified by prep-HPLC to give compound **4105** (20 mg, 10%). +ESI-MS:m/z 494.2[M +H]⁺.

EXAMPLE 37-1 Preparation of Compound 4200A



[1309] A mixture of **42-1** (6.00 g, 19.2 mmol), Pd(PPh₃)₂Cl₂ (133 mg, 0.19 mmol) and tributyl(1-ethoxyethenyl)stannane (6.0 mL, 17.7 mmol) in 1,4-dioxane (55 mL) was degassed and heated to 90°C. After 1.5 h, the mixture was diluted with EtOAc. The organic portion was washed twice with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 85:15) afforded **42-2** as a pale yellow solid (2.36 g, 54%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.56 (s, 3 H) 3.99 (s, 3 H) 7.66 (d, *J*=8.28 Hz, 1 H) 8.01 (d, *J*=8.53 Hz, 1 H).

[1310] A mixture of **42-2** (2.36 g, 10.3 mmol), (3-chloro-4-fluorophenyl)boronic acid (2.70 g, 15.4 mmol), Pd(dppf)Cl₂ (500 mg, 0.721 mmol) and aq Na₂CO₃ (2M solution, 12.9 mL, 25.7 mmol) in DCE (30 mL) was degassed and heated to 85°C. After 1 h, the mixture was diluted with DCM and filtered through a pad of celite. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-EtOAc, 100:0 to 80:20) gave **42-3** as a white solid (1.70 g, 60%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.65 (s, 3 H) 3.98 (s, 3 H) 7.55 (t, *J*=8.91 Hz, 1 H) 7.75 (d, *J*=8.78 Hz, 1 H) 7.96 - 8.08 (m, 2 H) 8.16 (dd, *J*=7.40, 2.13 Hz, 1 H).

[1311] Br₂ (500 uL, 10.0 mmol) was added to a mixture of **42-3** (1.70 g, 6.1 mmol) in 30% HBr-acetic acid (6.6 mL), which had been pre-cooled to 0°C. The mixture was stirred at 0°C for 1 h, then allowed to reach rt and stirred for 1.5 h. The mixture was poured into cold saturated aq. NaHCO₃ solution. The aqueous portion was extracted twice with DCM. The combined organic portions were dried (Na₂SO₄) and filtered. The volatiles were removed under reduced pressure. Chromatography of the residue (cyclohexane-DCM, 75:25 to 60:40) afforded **42-4** as a white solid (935 mg, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.99 (s, 3 H) 5.08 (s, 2 H) 7.55 (t, *J*=9.03 Hz, 1 H) 7.77 - 7.81 (m, 1 H) 8.03 - 8.11 (m, 2 H) 8.21 (dd, *J*=7.40, 2.13 Hz, 1 H).

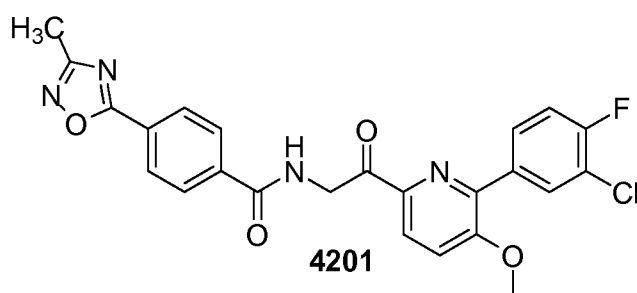
[1312] NaBH₄ (109 mg, 2.86 mmol) was added to a solution of **42-4** (930 mg, 2.60 mmol) in MeOH (20 mL), which had been pre-cooled to 0°C. The mixture warmed to rt. After 30 mins, a 1M aq HCl solution was added and the methanolic portion was removed under reduced pressure. The aqueous phase was extracted 3 times with DCM. The combined organic portions were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Crude **42-5** (887 mg) was in without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.74 (dd, *J*=10.1, 6.1 Hz, 1 H) 3.83 -

3.93 (m, 4 H) 4.81 - 4.93 (m, 1 H) 5.96 (d, $J=5.2$ Hz, 1 H) 7.44 - 7.54 (m, 2 H) 7.63 (d, $J=8.5$ Hz, 1 H) 7.98 (ddd, $J=8.7, 4.9, 2.1$ Hz, 1 H) 8.12 (dd, $J=7.4, 2.1$ Hz, 1 H).

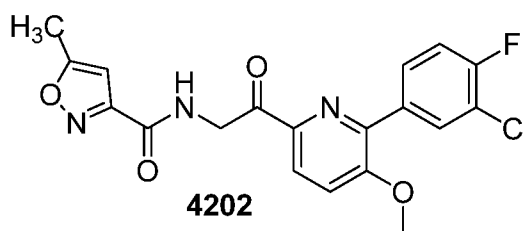
[1313] A mixture of **42-5** (870 mg) in 7M NH_3 -MeOH (28 mL) was stirred at rt for 36 h. The volatiles were removed under reduced pressure. The residue was purified by reverse phase chromatography (water- CH_3CN , 80:20 to 60:40) to afford **42-6** as a white solid (472 mg, 61% over two steps). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.03 (dd, $J=12.7, 8.9$ Hz, 1 H), 3.27 (dd, $J=12.7, 3.4$ Hz, 1 H), 3.90 (s, 3 H), 4.79 - 4.92 (m, 1 H), 6.20 (d, $J=4.8$ Hz, 1 H), 7.46 - 7.57 (m, 2 H), 7.68 (d, $J=8.8$ Hz, 1 H), 7.84 - 7.84 (m, 1 H), 7.90 (br. s., 2 H), 7.98 (ddd, $J=8.7, 4.9, 2.3$ Hz, 1 H), 8.10 (dd, $J=7.5, 2.0$ Hz, 1 H).

[1314] A mixture of **42-6** (50.0 mg, 0.168 mmol), EDC (48.0 mg, 0.252 mmol), HOBT (34.0 mg, 0.252 mmol), TEA (50 μL , 0.336 mmol) and acid (0.201 mmol) in DCM (1 mL) was stirred at rt for 1 h. The mixture was washed with 1M aq HCl solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Compound **42-7** was used in the next step without further purification.

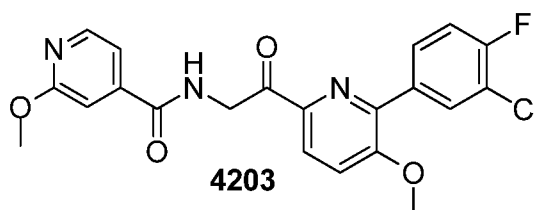
[1315] Dess-Martin periodinane (0.252 mmol) was added to a solution of **42-7** in DCM (2 mL). The mixture was stirred at rt for 1 h. A 1:1 saturated aq NaHCO_3 solution-saturated aq $\text{Na}_2\text{S}_2\text{O}_3$ solution was added. The mixture was stirred at rt for 30 mins and the layers were separated. The organic portion was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue afforded compound **4200A**.



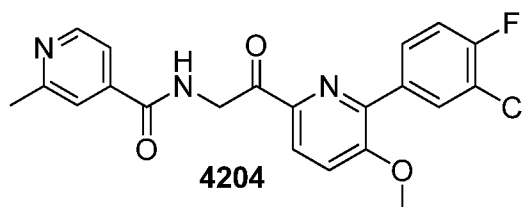
[1316] Compound **4201** was prepared by coupling **42-6** with 4-(3-methyl-1,2,4-oxadiazol-5-yl)benzoic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4201** was obtained as an off-white solid (10% over two steps). UPLC/MS(ES^+), m/z 481.15 $[\text{M}+\text{H}]^+$.



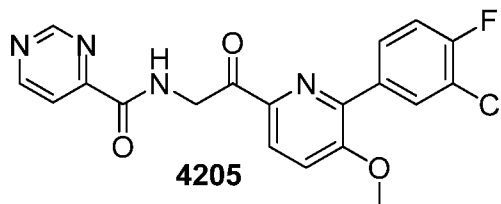
[1317] Compound **4202** was prepared by coupling **42-6** with 5-methyl-1,2-oxazole-3-carboxylic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4202** was obtained as a white solid (31% over two steps). UPLC/MS(ES^+), m/z : 404.10 $[\text{M}+\text{H}]^+$.



[1318] Compound **4203** was prepared by coupling **42-6** with 2-methoxypyridine-4-carboxylic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4203** was obtained as a pale yellow solid (14% over two steps). UPLC/MS(ES^+), m/z : 430.21 $[\text{M}+\text{H}]^+$.

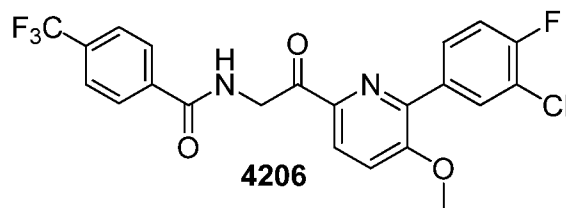


[1319] Compound **4204** was prepared by coupling **42-6** with 2-methylpyridine-4-carboxylic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4204** was obtained as an off-white solid (24% over two steps). UPLC/MS(ES^+), m/z : 414.10 $[\text{M}+\text{H}]^+$.

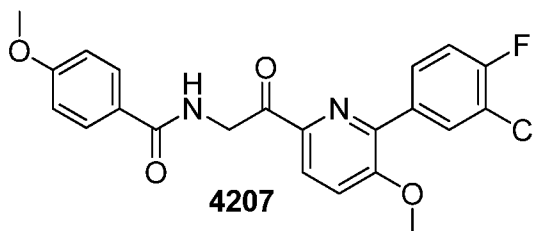


[1320] Compound **4205** was prepared by coupling **42-6** with pyrimidine-4-carboxylic acid followed by DMP oxidation, and by following a synthetic route, which

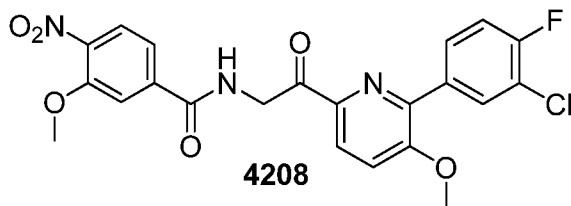
closely follows that described for preparation of compound **4200A**. Compound **4205** was obtained as a pale yellow solid (25% over two steps). UPLC/MS(ES^+), m/z : 401.15 $[\text{M}+\text{H}]^+$.



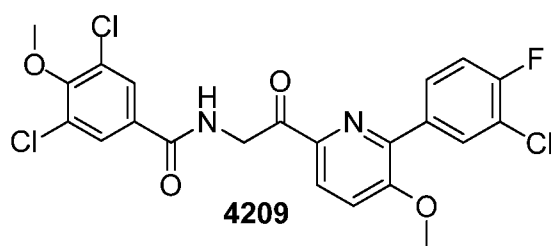
[1321] Compound **4206** was prepared by coupling **42-6** with 4-(trifluoromethyl)benzoic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4206** was obtained as an off-white solid (48% over two steps). UPLC/MS(ES^+), m/z : 467.18 $[\text{M}+\text{H}]^+$.



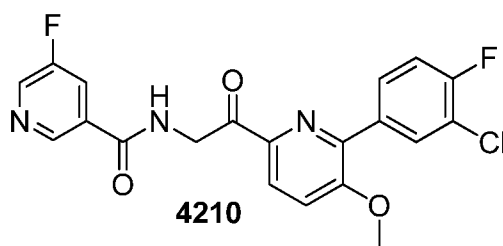
[1322] Compound **4207** was prepared by coupling **42-6** with 4-methoxybenzoic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4207** was obtained as a white solid (61% over two steps). UPLC/MS(ES^+), m/z : 429.22 $[\text{M}+\text{H}]^+$.



[1323] Compound **4208** was prepared by coupling **42-6** with 3-methoxy-4-nitrobenzoic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4208** was obtained as a white solid (70% over two steps). UPLC/MS(ES^+), m/z : 474.20 $[\text{M}+\text{H}]^+$.

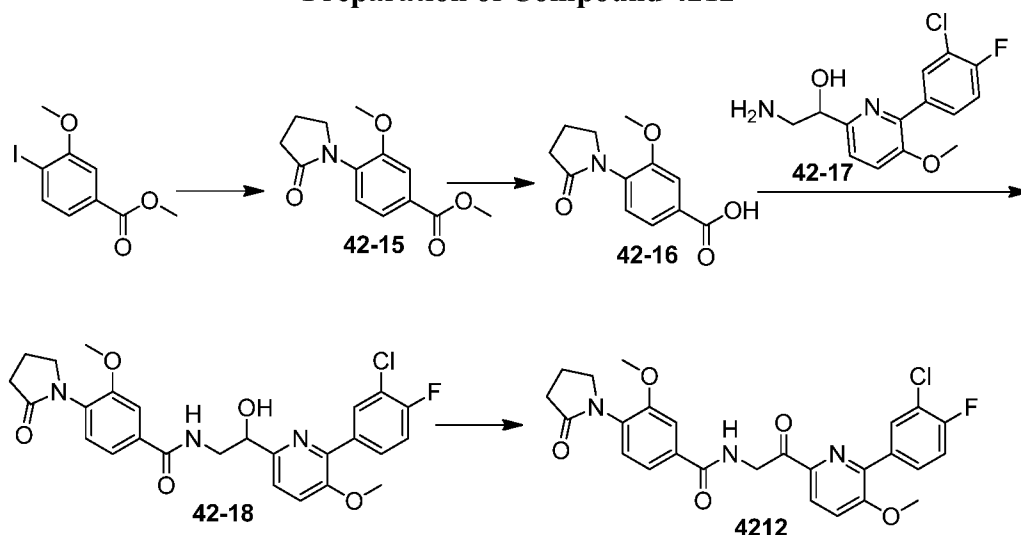


[1324] Compound **4209** was prepared by coupling **42-6** with 3,5-dichloro-4-methoxybenzoic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4209** was obtained as a white solid (52% over two steps). UPLC/MS(ES⁺), m/z: 497.09 [M+H]⁺.



[1325] Compound **4210** was prepared by coupling **42-6** with 5-fluoropyridine-3-carboxylic acid followed by DMP oxidation, and by following a synthetic route, which closely follows that described for preparation of compound **4200A**. Compound **4210** was obtained as a white solid (31% over two steps). UPLC/MS(ES⁺), m/z: 418.16 [M+H]⁺.

EXAMPLE 37-2 **Preparation of Compound 4212**



[1326] 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

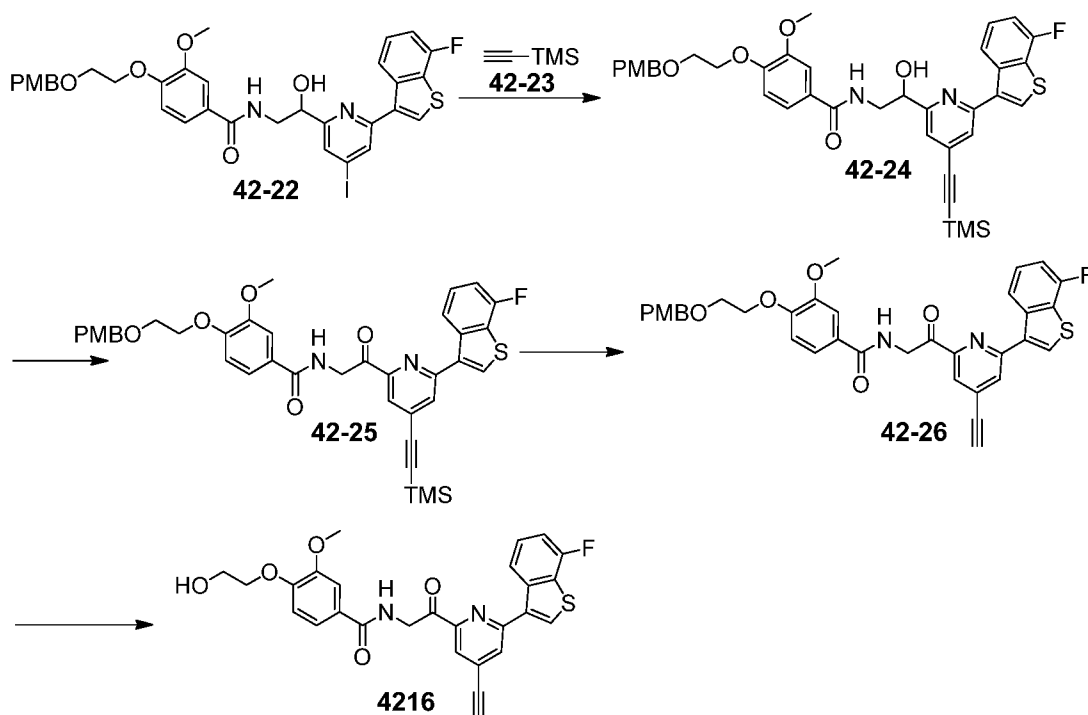
g, 2.2 mmol), xantphos (25 mg, 0.43 mmol) and tris(dibenzylideneacetone)dipalladium(0) (40 mg, 0.43 mmol). The mixture was heated at 110°C for 3 h. The mixture was then diluted with EA. The organic phase was washed with water, 1N HCl, NaHCO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **42-15** (0.178 g, 83%). LC/MS: [M+H] 478.10.

[1327] To a solution of **42-15** (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 Na₂SO₄ to give **42-16** (0.152 g, 90%). ¹H NMR (400 MHz, CDCl₃): 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).

[1328] To a solution of **42-16** (0.152 g, 0.65 mmol), **42-17** (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 rt. The mixture was diluted with EA. The organic phase was washed with water, 1N HCl, NaHCO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by chromatography on silica gel (EA/hexane) to give **42-18** (0.172 g, 51%). LC/MS: [M+H] 478.10.

[1329] Dess-Martin periodinane (220 mg, 0.50 mmol) was added to a solution of **42-18** (172 mg, 0.34 mmol) in CH₂Cl₂, and the mixture was stirred for 2 h. The mixture was diluted with CH₂Cl₂ and washed with saturated Na₂CO₃, and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EA/hexane) to give compound **4212** (77 mg, 45%) as white solid. LC/MS: [M+H] 512.10.

EXAMPLE 37-3
Preparation of Compound 4216



[1330] To a mixture of **42-22** (200 mg, 0.275 mmol) in THF (5 mL), was added **42-23** (41.2 mg, 0.42 mmol), Et₃N (110.46 mg, 1.09 mmol), CuI (1.04 mg, 0.0055 mmol) and Pd(PPh₃)₄ (6.34 mg, 0.0055 mol). The mixture was bubbled with nitrogen gas and stirred at rt for 1 h. The mixture was washed with water and extracted with EA. The organic layer was dried over anhydrous sodium sulfate, and concentrated in vacuum. The residue was purified by column chromatography to provide **42-24** (130 mg, 66.9%). +ESI-MS:m/z: 699.2 [M + H]⁺.

[1331] To a solution of **42-24** (110 mg, 0.158 mmol) in DCM (10 mL) was added DMP (135 mg, 0.315 mmol). The mixture was stirred at rt overnight. The solution was then washed with water and extracted with EA. The organic layer was dried over sodium sulfate, concentrated in vacuum to give the desired residue, which was purified by column chromatography to give the desired **42-25** as a white solid (100 mg, 90.8%). +ESI-MS:m/z: 670.2 [M + H]⁺.

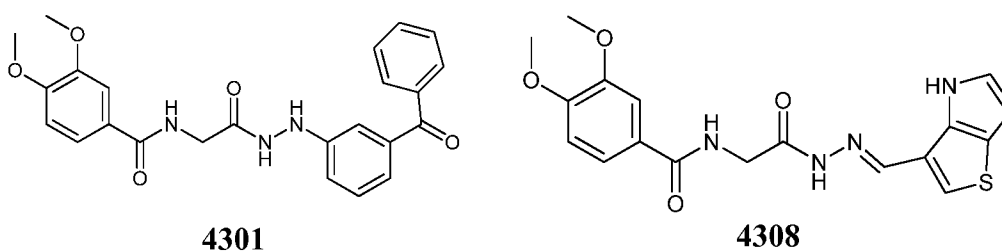
[1332] To a solution of **42-25** (140 mg, 0.20 mmol) in MeOH/THF (1:1, 4 mL) was added KF (13.99 mg, 0.24 mmol). The mixture was stirred at rt for 1 h. The mixture was diluted with water, and extracted with EA. The organic layer was dried over anhydrous

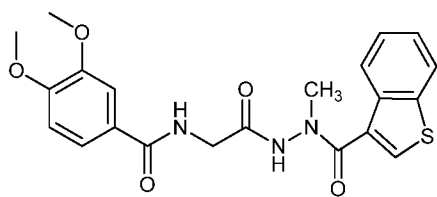
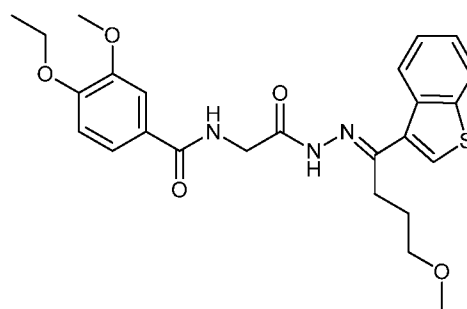
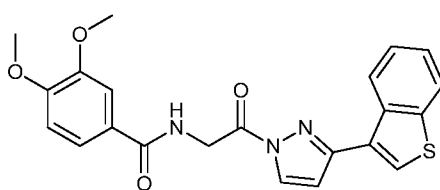
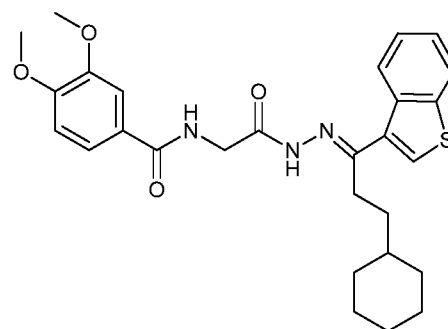
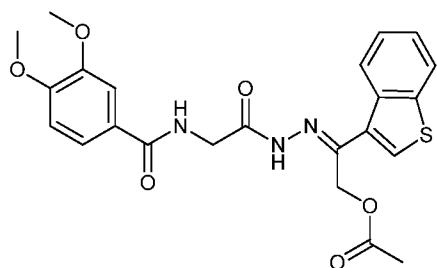
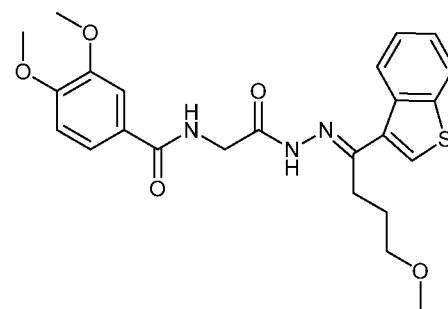
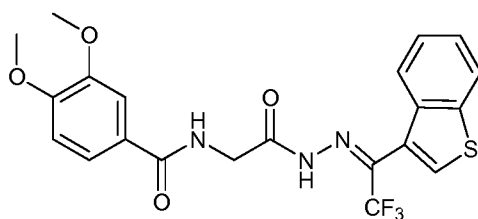
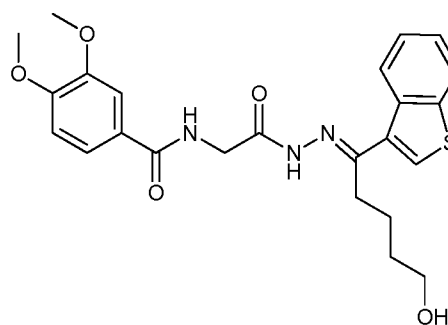
sodium sulfate, and concentrated in vacuum to give **42-26** as a white solid (120 mg, 96.0%). +ESI-MS:m/z : 625.1 [M +H]⁺.

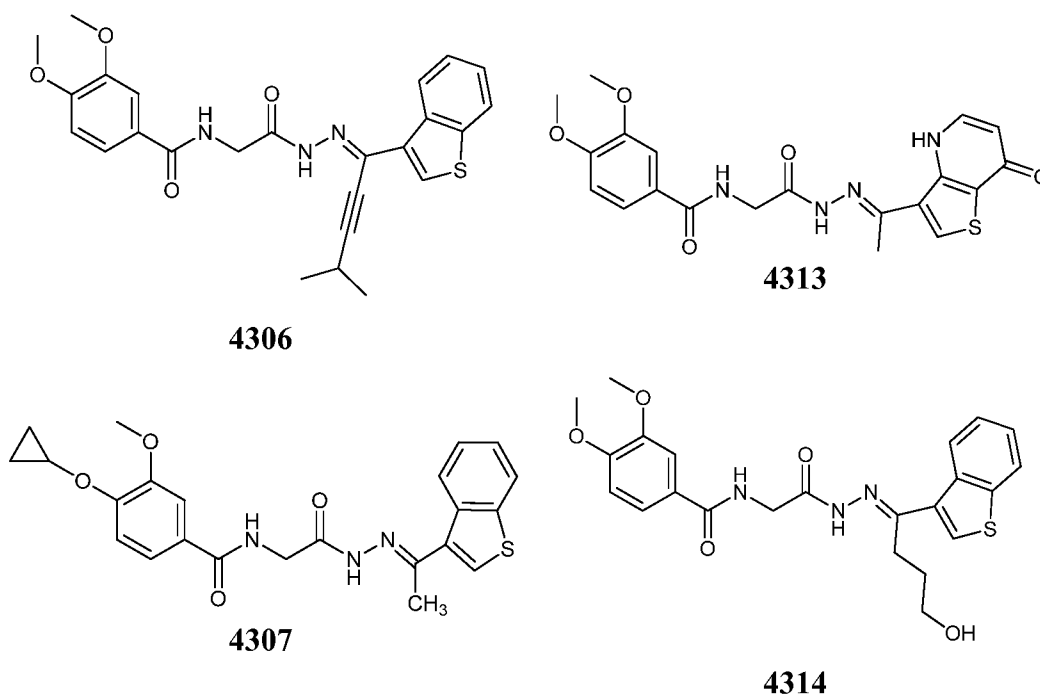
[1333] To a solution of **42-26** (110 mg, 0.18 mmol) in DCM (3 mL) was added TFA (3 mL), and stirred at rt for 10 mins. The mixture was diluted with EA, and washed with NaHCO₃ solution. The organic layer was dried over anhydrous sodium sulfate, and concentrated at low pressure to give the crude product, which was purified by prep-HPLC to give compound **4216** (9.3 mg, 10.2%). +ESI-MS:m/z: 504.9 [M +H]⁺.

[1334] The foregoing syntheses are exemplary and can be used as a starting point to prepare a number of additional compounds. Additional compounds of Formula (I) and Formula (II) are shown in Table 1. These compounds can be prepared in various ways, including those synthetic schemes shown and described herein. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

Table 1



**4302****4309****4303****4310****4304****4311****4305****4312**



EXAMPLE A **RSV Antiviral Assay**

[1335] CPE reduction assays are performed as described by Sidwell and Huffman et al., Appl. Microbiol. (1971) 22(5):797–801 with slight modifications. HEp-2 cells (ATCC#, CCL-23) are seeded at a density of 1,500 cells/30 μ l/well into the 384-well cell plate(s) (Corning#3701) one day prior to the assay. Compounds are added into 384-well cell plates by Labcyte POD 810 Plate Assembler system. Each of the test compounds is provided to duplicate wells of a 384-well cell plate at final concentrations starting from 100 μ M or 1 μ M using 1/3 stepwise dilutions for 9 points. Quick-thaw Respiratory Syncytial Virus (RSV) long strain (ATCC#VR-26) stock in a 37°C water bath. Place on ice until ready to use. Viruses are diluted to the concentration of 100 TCID₅₀/30 μ l with medium and 30 μ l diluted RSV are added into related wells of 384-well cell plates. For each plate, sixteen wells are set aside as uninfected, untreated cell controls (CC), and nine wells per test plate receive virus only as a control for virus replication (VC). The final DMSO concentration of all wells is 1%. Place the plates at 37°C, 5% CO₂ for 5 days.

[1336] After 5 days incubation, observe the CPE of cells in all wells. Cell controls should be natural and have no cell fusion; Cells in the virus control wells should

exhibit signs of virus cytopathology (giant cell formation, syncytia). Six μ l of cell counting kit-8 reagent (CCK-8, Dojindo Molecular Technologies Inc., CK04-20) are added to each well, which allows colorimetric assays to determine the number of viable cells through the dehydrogenase activity detection. After 3-4 hour incubation, the absorbance of each well is measured with a spectrophotometric plate reader at 450 nm wavelength, using a 630 nm filter as background according to manufacturer's instruction. The 50% effective concentration (EC_{50}) is calculated by using regression analysis, based on the mean O.D. at each concentration of compound.

[1337] Compounds of Formula (I) and Formula (II) are active in the assay against the RSV virus as demonstrated in Tables 2 and 3. Table 2 includes compounds with an EC_{50} value that is less than 1 μ M. Table 3 includes compounds with an EC_{50} value that is equal to or higher than 1 μ M and less than 50 μ M. Other tested compounds disclosed herein had an EC_{50} value of 50 μ M or greater.

Table 2

Compound	Compound	Compound	Compound	Compound	Compound
238	488	603B	1244	1329	1606
246A	490	604	1245	1332	1607
300	492	605	1247	1333	1608
411	493	650	1250	1334	1609
415	494	651	1252	1335	1612
423	400-1	1101	1253	1336	1613
427	400-4	1200	1255	1342	1614
446	400-7	1209	1256	1343	1616
455A	400-15	1211	1300	1358	1618
457	400-23	1213	1309	1359	1622
458A	400-25	1214	1310	1360	1623
459	400-26	1216	1312	1505	1803
460	502	1217	1316	1508	1806
461	510	1220	1318	1515	1807
462A	513	1221	1319	1525	1808
462B	514A	1227	1322	1529	1809
463A	514B	1232	1323	1531	1812
463B	600	1235	1325	1601	1816
464	601	1236	1326	1602	1819
475	602	1237	1327	1603	1821
476	603A	1241	1328	1605	1824

Compound	Compound	Compound	Compound	Compound	Compound
1825	1839	2111	2302	2638	3501
1830	2103	2112	2613	2641	3800
1831	2104	2115	2617	2646	3903
1832	2106	2200	2621	2648	4002
1835	2108	2300	2625	3302	
1837	2109	2301	2627	3500	

Table 3

Compound	Compound	Compound	Compound	Compound	Compound
215	453	400-13	1218	1338	1522
231	454	400-14	1223	1340	1523
235	456	400-16	1224	1341	1524
238	466	400-17	1225	1344	1526
245	467	400-18	1226	1345	1527
247	468	400-19	1228	1346	1528
400	469	400-21	1230	1351	1530
401	470	400-22	1238	1352	1532
402	471	400-24	1239	1353	1533
403	474	400-27	1240	1355	1534
409	477	400-28	1242	1356	1535
413	478	500	1243	1401	1536
414	479	501	1246	1402	1537
418	480	503	1248	1403	1538
422	481	504	1249	1404	1539
426	482	505	1251	1405	1540
430	483	506	1257	1502	1541
434	486	507	1258	1503	1604
436	489	508	1301	1504	1610
438	491	509	1302	1506	1611
439	495	511	1303	1507	1615
440	496	512	1307	1509	1619
441	497	606	1308	1510	1620
442	498	839	1311	1511	1621
443	400-2	840	1313	1512	1700
444	400-3	911	1314	1513	1701
445	400-5	1100	1315	1514	1800
447	400-6	1202	1317	1516	1801
448A	400-8	1204	1320	1517	1822
449	400-9	1205	1321	1518	1836
450	400-10	1206	1330	1519	1900
451	400-11	1210	1331	1520	2100
452	400-12	1215	1337	1521	2101

Compound	Compound	Compound	Compound	Compound	Compound
2102	2305	2604	2703	3101	4105
2105	2306	2642	2800	3103	4202
2107	2504	2647	2801	3300	4204
2203	2507	2649	2802	3401	4205
2303	2600	2651	2803	3900	4216
2304	2601	2701	3100	3901	

EXAMPLE B **Cytotoxicity Determination**

[1338] 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% CO₂ for 5 days. Add 6 μl CCK-8 into each well and incubate in a CO₂ incubator at 37°C for 3-4 hours. Read the plates to obtain the optical densities which are used to calculate 50% cytotoxicity concentration (CC₅₀).

[1339] Compounds of Formula (I) and Formula (II) are not cytotoxic as shown in Tables 4 and 5. Table 4 includes compounds with a CC₅₀ value that is greater than 100 μM . Table 5 includes compounds with a CC₅₀ value that is equal to or less than 100 μM and greater than 10 μM . Other tested compounds disclosed herein had a CC₅₀ value of less than 10 μM .

Table 4

Compound	Compound	Compound	Compound	Compound	Compound
101	400-15	423	440	455A	473
215	400-16	424	441	456	475
235	400-18	425	442	459	476
242	400-21	427	443	460	477
243	400-23	428	444	462A	480
247	400-24	429	445	463A	481
400-1	400-25	430	446	463B	488
400-3	400-26	431	447	464	490
400-5	400-27	434	449	466	491
400-6	400-28	435	450	467	492
400-10	403	436	451	468	493
400-13	420	438	452	470	494
400-14	421	439	454	471	497

Compound	Compound	Compound	Compound	Compound	Compound
498	1201	1300	1402	1603	2205
500	1202	1302	1403	1604	2301
502	1204	1308	1404	1606	2303
503	1207	1309	1502	1609	2306
508	1208	1310	1504	1610	2601
513	1210	1311	1505	1611	2604
514A	1211	1312	1508	1612	2613
514B	1213	1316	1509	1613	2617
600	1215	1317	1514	1614	2621
601	1217	1318	1515	1615	2625
602	1218	1319	1517	1616	2627
603A	1219	1320	1520	1618	2641
603B	1220	1322	1524	1619	2642
604	1221	1325	1525	1621	2647
650	1222	1326	1526	1622	2648
651	1224	1327	1527	1623	2802
839	1225	1328	1528	1700	2803
840	1235	1329	1529	1701	2900
904	1236	1330	1530	1801	2901
906	1238	1336	1531	1806	3200
907	1239	1337	1533	1807	3300
908	1240	1340	1534	1816	3401
909	1243	1341	1535	1824	3500
913	1245	1342	1536	1825	3900
914	1249	1343	1537	1830	3903
915	1250	1345	1538	2101	4103
916	1251	1346	1539	2108	4104
917	1252	1351	1540	2111	4202
1000	1253	1353	1541	2112	4204
1101	1257	1356	1601	2200	4205
1200	1258	1360	1602	2203	

Table 5

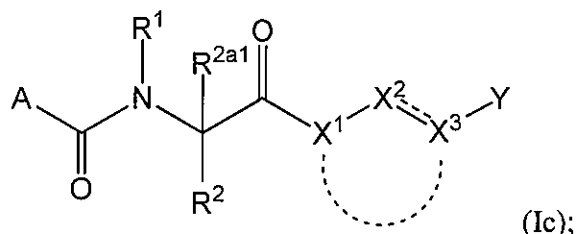
Compound	Compound	Compound	Compound	Compound	Compound
119	241	409	417	437	465
215	245	411	418	448A	469
231	246A	412	419	453	472
236	300	413	422	457	474
237	400	414	426	458A	478
238	401	415	432	461	479
240	402	416	433	462B	482

Compound	Compound	Compound	Compound
483	1232	1521	2800
486	1233	1522	2801
487	1234	1532	3100
489	1237	1605	3101
495	1241	1607	3102
496	1242	1608	3103
400-2	1244	1620	3201
400-4	1246	1800	3302
400-7	1247	1803	3501
400-8	1248	1808	3800
400-9	1255	1809	3901
400-11	1256	1812	4002
400-12	1301	1819	4102
400-17	1303	1821	4105
400-19	1304	1822	
400-22	1313	1831	
501	1314	1832	
504	1315	1835	
505	1321	1836	
509	1323	1837	
510	1331	1839	
511	1332	1900	
512	1333	2100	
605	1334	2102	
606	1335	2103	
700	1338	2104	
860	1339	2105	
902	1344	2106	
910	1352	2107	
911	1354	2109	
912	1355	2115	
1100	1358	2204	
1205	1401	2300	
1206	1405	2302	
1209	1503	2304	
1214	1506	2305	
1216	1507	2600	
1223	1510	2638	
1226	1511	2646	
1227	1513	2649	
1228	1516	2651	
1230	1518	2701	
1231	1519	2703	

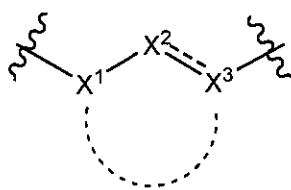
[1340] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the 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.

CLAIMS

1. A compound characterized by having the structure of Formula (Ic), or a pharmaceutically acceptable salt thereof, having the structure:



wherein X^1 , X^2 and X^3 are each independently C (carbon), N (nitrogen), or O (oxygen), and the



dotted line between X^1 and X^3 of indicates an optionally substituted 6 membered mono-cyclic heteroaryl, by joining X^1 and X^3 together; with the proviso that the valencies of X^1 , X^2 and X^3 are satisfied with a substituent selected from the group consisting of hydrogen and an optionally substituted C_{1-4} alkyl; and X^1 , X^2 and X^3 are uncharged;

wherein:

A is selected from the group consisting of an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted C_{6-10} aryl, an optionally substituted C_{6-10} 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 C_{6-10} aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

R^1 is hydrogen or an unsubstituted C_{1-4} alkyl;

R^2 and R^{2a1} are each independently selected from the group consisting of hydrogen, an optionally substituted C_{1-4} alkyl, alkoxyalkyl, aminoalkyl, hydroxyalkyl, hydroxy, an optionally substituted C_{6-10} aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl); or

R^1 and R^2 , together with the atoms to which they are attached, are joined to form an optionally substituted 5-membered heterocyclic ring or an optionally substituted 6-membered heterocyclic ring,

wherein when a group is optionally substituted, unless otherwise specified, the group may be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acylalkyl, alkoxyalkyl, aminoalkyl, amino acid, C_{6-10} aryl, heteroaryl, heterocyclyl, C_{6-10} aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, 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-alkyl amine and a di-alkyl amine;

wherein "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, wherein the ring system has a fully delocalized pi-electron system and contains one or more heteroatoms selected from nitrogen, oxygen and sulfur, and wherein the heteroaryl contains 4 to 14 atoms in the ring(s); and

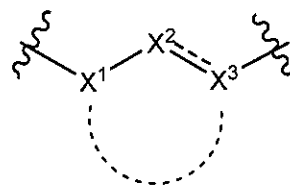
wherein "heterocyclyl" refers to a 3 to 18-membered monocyclic, bicyclic, and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur constitute said ring system; wherein the heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings; wherein the heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems; wherein when composed of two or more rings, the rings may be joined together in a fused fashion; and wherein any nitrogens in the heterocyclyl may be quaternized.

2. The compound of Claim 1, wherein R^1 is hydrogen.
3. The compound of Claim 1, wherein R^1 is an unsubstituted C_{1-4} alkyl.
4. The compound of any one of Claims 1-3, wherein both R^2 and R^{2a1} are hydrogen.
5. The compound of any one of Claims 1-3, wherein R^2 is hydrogen; and R^{2a1} is an unsubstituted C_{1-4} alkyl.

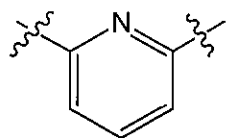
6. The compound of any one of Claims 1-3, wherein R^2 is hydrogen; and R^{2a1} is a substituted C_{1-4} alkyl.

7. The compound of Claim 1, wherein R^2 is hydrogen and R^{2a1} is an optionally substituted C_{6-10} aryl(C_{1-6} alkyl), an optionally substituted heterocyclyl(C_{1-6} alkyl), an alkoxyalkyl, an aminoalkyl or a hydroxyalkyl; or R^{2a1} is hydrogen and R^1 and R^2 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.

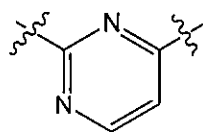
8. The compound of any one of Claims 1-3, wherein R^2 is hydrogen and R^{2a1} is hydroxy.



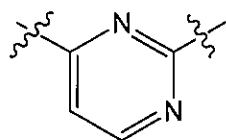
9. The compound of any one of Claims 1-8, wherein the Formula (Ic) is selected from the group consisting of: an optionally substituted



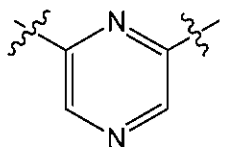
, an optionally substituted



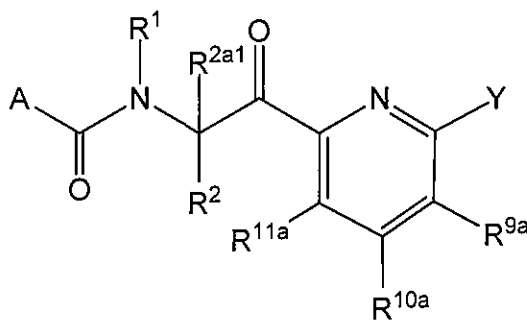
, an optionally substituted



, and an optionally substituted



10. The compound of any one of Claims 1-9, wherein the compound of Formula (Ic)



is a compound of Formula (Id):

(Id)

wherein: R^{9a} , R^{10a} and R^{11a} 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 C_{6-10} aryl, an optionally substituted heteroaryl, an optionally substituted

heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, amino, mono-alkyl amine, di-alkyl amine, halo(C₁₋₈ alkyl) and an optionally substituted C-carboxy.

11. The compound of Claim 10, wherein R^{9a} is selected from the group consisting of hydrogen, hydroxy, an optionally substituted C₁₋₈ alkyl, an optionally substituted C₁₋₈ alkoxy, an optionally substituted alkoxyalkyl, mono-alkyl amine and di-alkyl amine.

12. The compound of Claim 10 or 11, wherein R^{10a} is selected from the group consisting of hydrogen, halogen, an optionally substituted C₁₋₈ alkyl, an optionally substituted C₂₋₈ alkenyl, an optionally substituted C₂₋₈ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₆₋₁₀ aryl, an optionally substituted 6 membered heterocyclyl, an optionally substituted hydroxyalkyl, an optionally substituted C₁₋₈ alkoxy, mono-alkyl amine, di-alkyl amine, halo(C₁₋₈ alkyl) and an optionally substituted C-carboxy.

13. The compound of any one of Claims 10-12, wherein R^{11a} is selected from the group consisting of hydrogen, hydroxy and an optionally substituted C₁₋₈ alkoxy.

14. The compound of any one of Claims 1-13, wherein A of Formula (Ic) is selected from the group consisting of:

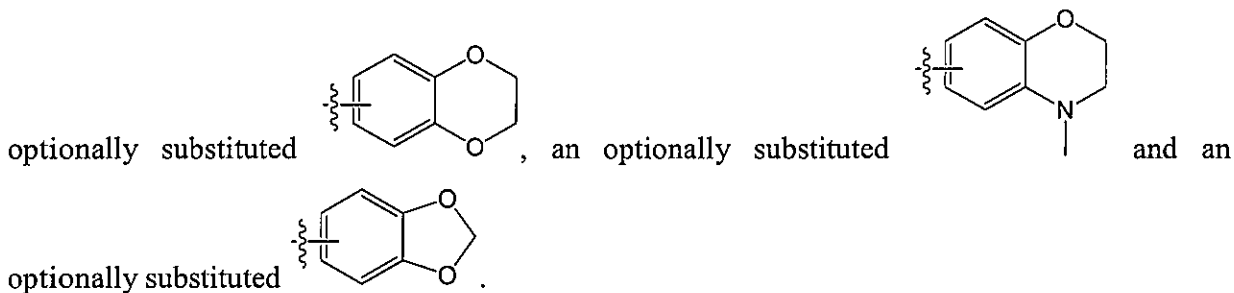
an optionally substituted C₃₋₈ monocyclic cycloalkyl,

an optionally substituted C₆₋₁₀ aryl,

an optionally substituted C₆₋₁₀ aryl(C₁₋₂ alkyl),

an optionally substituted monocyclic heteroaryl 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 oxazole and an optionally substituted isoxazole; and

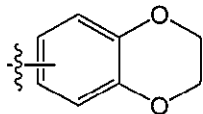
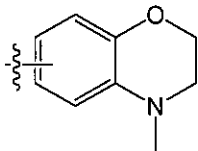
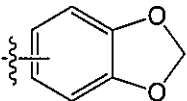
an optionally substituted bicyclic heterocyclyl selected from the group consisting of an



15. The compound of any one of Claims 1-14, wherein when A of Formula (Ic) is substituted, A is substituted with one or more substituents selected from the group consisting of an unsubstituted C₁₋₄ alkyl, cycloalkyl, hydroxy, an optionally substituted C₁₋₄ alkoxy, halogen, haloalkyl, a haloalkoxy, nitro, amino, mono-alkyl amine, di-alkyl amine, sulphenyl, alkoxyalkyl, phenyl, mono-cyclic heteroaryl, mono-cyclic heterocyclyl and aminoalkyl.

16. The compound of any one of Claims 1-15, wherein A of Formula (Ic) is selected from the group consisting of an optionally substituted C₃₋₈ monocyclic cycloalkyl and an optionally substituted C₆₋₁₀ aryl(C₁₋₂ alkyl).

17. The compound of any one of Claims 1-15, wherein A of Formula (Ic) is an optionally substituted monocyclic heteroaryl 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 oxazole and an optionally substituted isoxazole; or an optionally substituted bicyclic

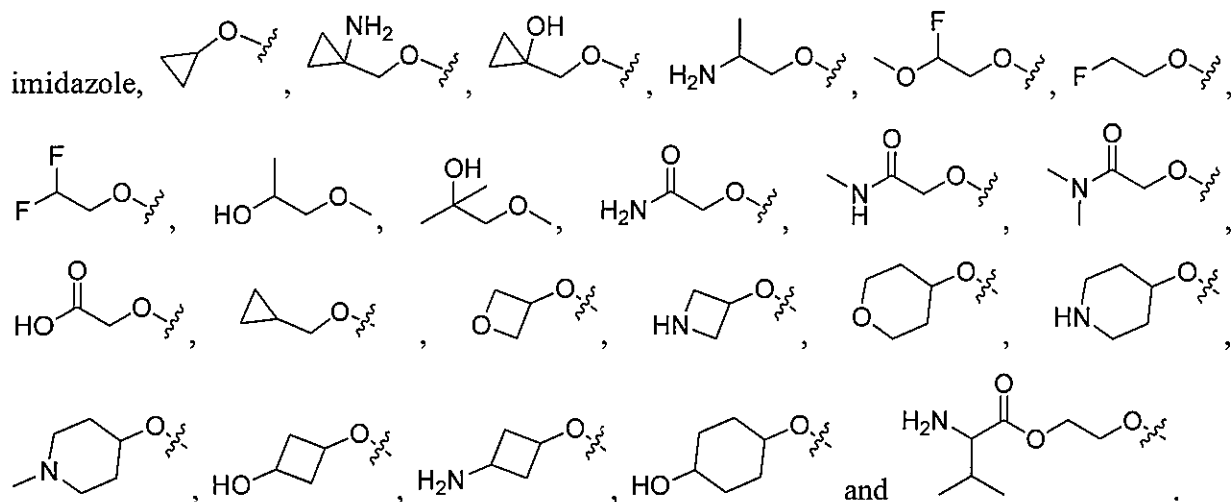
heterocyclyl selected from the group consisting of an optionally substituted , an optionally substituted  and an optionally substituted .

18. The compound of any one of Claims 1-15, wherein A of Formula (Ic) is an optionally substituted C₆₋₁₀ aryl.

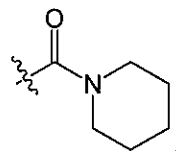
19. The compound of Claim 18, wherein A of Formula (Ic) is an optionally substituted phenyl.

20. The compound of Claim 19, wherein the phenyl is substituted with one or more substituents selected from the group consisting of methyl, ethyl, propyl, butyl, hydroxy, methoxy, ethoxy, propoxy, butoxy, phenoxy, bromo, chloro, fluoro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, N,N-di-methyl-amino, N,N-di-ethyl-amino, N-methyl-N-ethyl-amino, N-methyl-amino, N-ethyl-amino, amino, alkylthio, phenyl, imidazole, morpholinyl, pyrazole, pyrrolidinyl, pyridinyl, piperidinyl, pyrrolidinone, pyrimidine, pyrazine, 1,2,4-oxadiazole, -(CH₂)₁₋₂-NH(CH₃), -O(CH₂)₂-NH₂, -O(CH₂)₂-NH(CH₃), -O(CH₂)₂-N(CH₃)₂, -O-

(CH₂)₂₋₄OH, -O(CH₂)₂OCH₃, -O(CH₂)₁₋₂-morpholinyl, -O(CH₂)₁₋₂-triazole, -O(CH₂)₁₋₂-



21. The compound of any one of Claims 1-20, wherein when Y of Formula (Ic) is substituted, 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 C₁₋₄ alkyl, an unsubstituted C₂₋₄ alkenyl, an unsubstituted C₂₋₄ alkynyl, an optionally substituted C₆₋₁₀ aryl, an optionally substituted 5 or 6 membered heteroaryl, an optionally substituted 5 or 6 membered heterocyclyl, hydroxy, C₁₋₄ alkoxy, alkoxyalkyl, C₁₋₄ haloalkyl, haloalkoxy, an unsubstituted acyl, an optionally substituted -C-carboxy, an optionally substituted -C-amido, sulfonyl,



carbonyl, amino, mono-alkyl amine, di-alkyl amine and

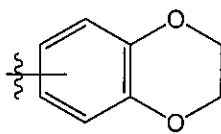
22. The compound of any one of Claims 1-21, wherein Y of Formula (Ic) is an optionally substituted phenyl.

23. The compound of Claim 22, wherein Y of Formula (Ic) is a substituted phenyl.

24. The compound of Claim 23, wherein Y of Formula (Ic) is a di-substituted phenyl.

25. The compound of Claim 24, wherein Y of Formula (Ic) is a di-halo substituted phenyl.

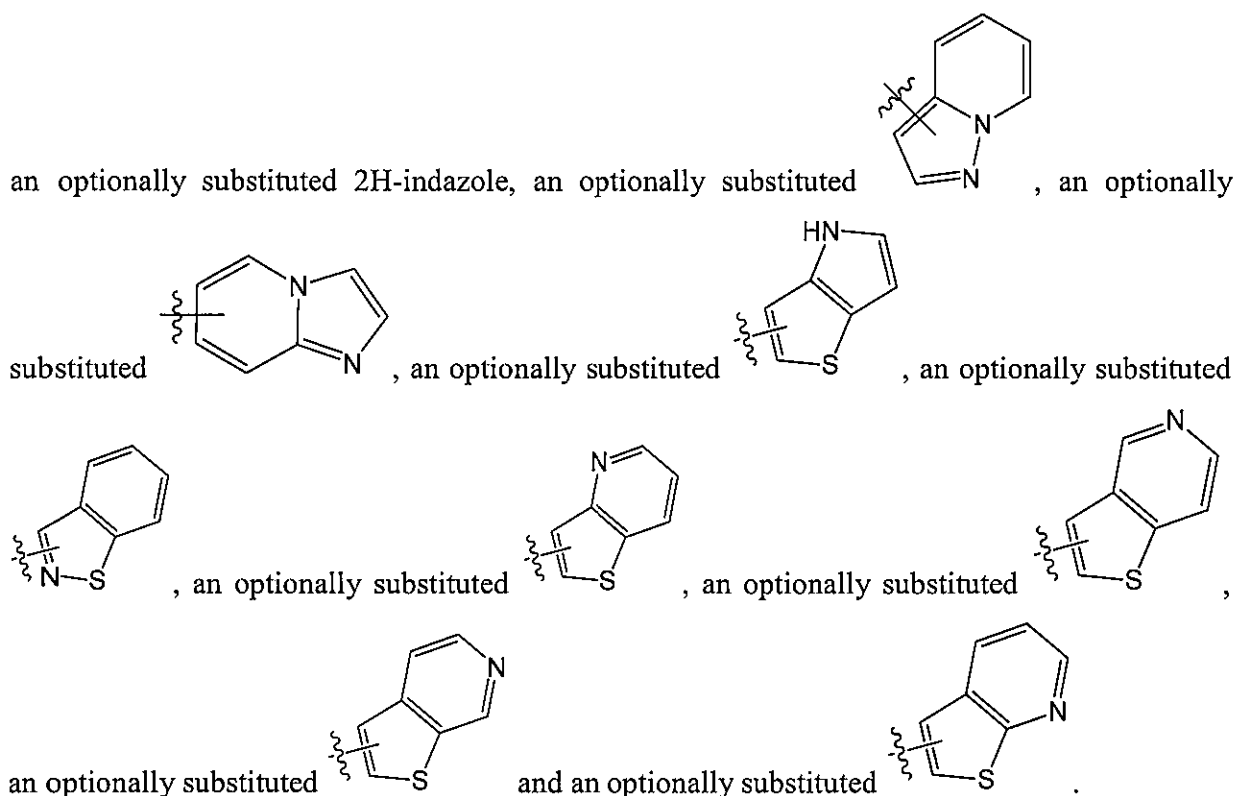
26. The compound of any one of Claims 1-21, wherein Y of Formula (Ic) is an



optionally substituted ; or an optionally substituted mono-cyclic heteroaryl

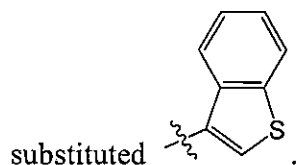
selected from the group consisting of an optionally substituted imidazole, an optionally substituted furan, an optionally substituted thiophene, an optionally substituted pyrrole, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted oxazole and an optionally substituted isoxazole.

27. The compound of any one of Claims 1-21, wherein Y of Formula (Ic) is an optionally substituted bicyclic heteroaryl 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 benzoxazole, an optionally substituted benzoisoxazole, an optionally substituted benzoisothiazole, an optionally substituted benzothiazole, an optionally substituted benzoimidazole, an optionally substituted benzotriazole, an optionally substituted 1H-indazole,



28. The compound of Claim 27, wherein Y of Formula (Ic) is an optionally substituted benzothiophene.

29. The compound of Claim 28, wherein Y of Formula (Ic) is an optionally

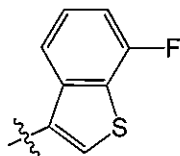


30. The compound of Claim 28 or 29, wherein Y of Formula (Ic) is an unsubstituted benzothiophene.

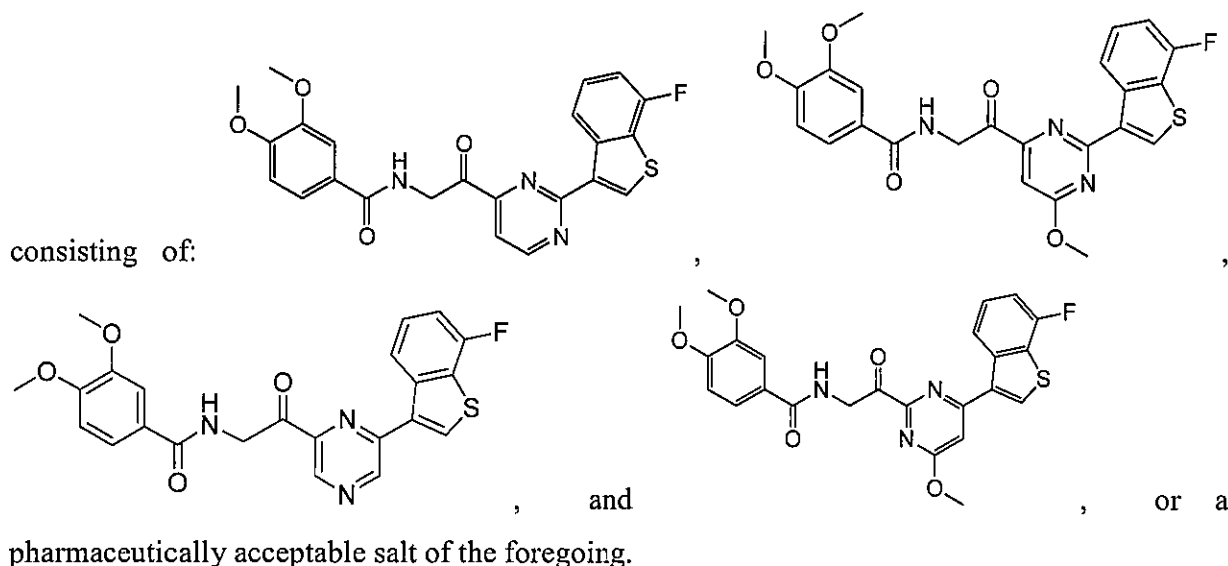
31. The compound of Claim 28 or 29, wherein Y of Formula (Ic) is a substituted benzothiophene.

32. The compound of Claim 31, wherein the benzothiophene is substituted with one or more substituents selected from the group consisting of halogen, carbonyl, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, cyano, amino and mono-alkyl amine.

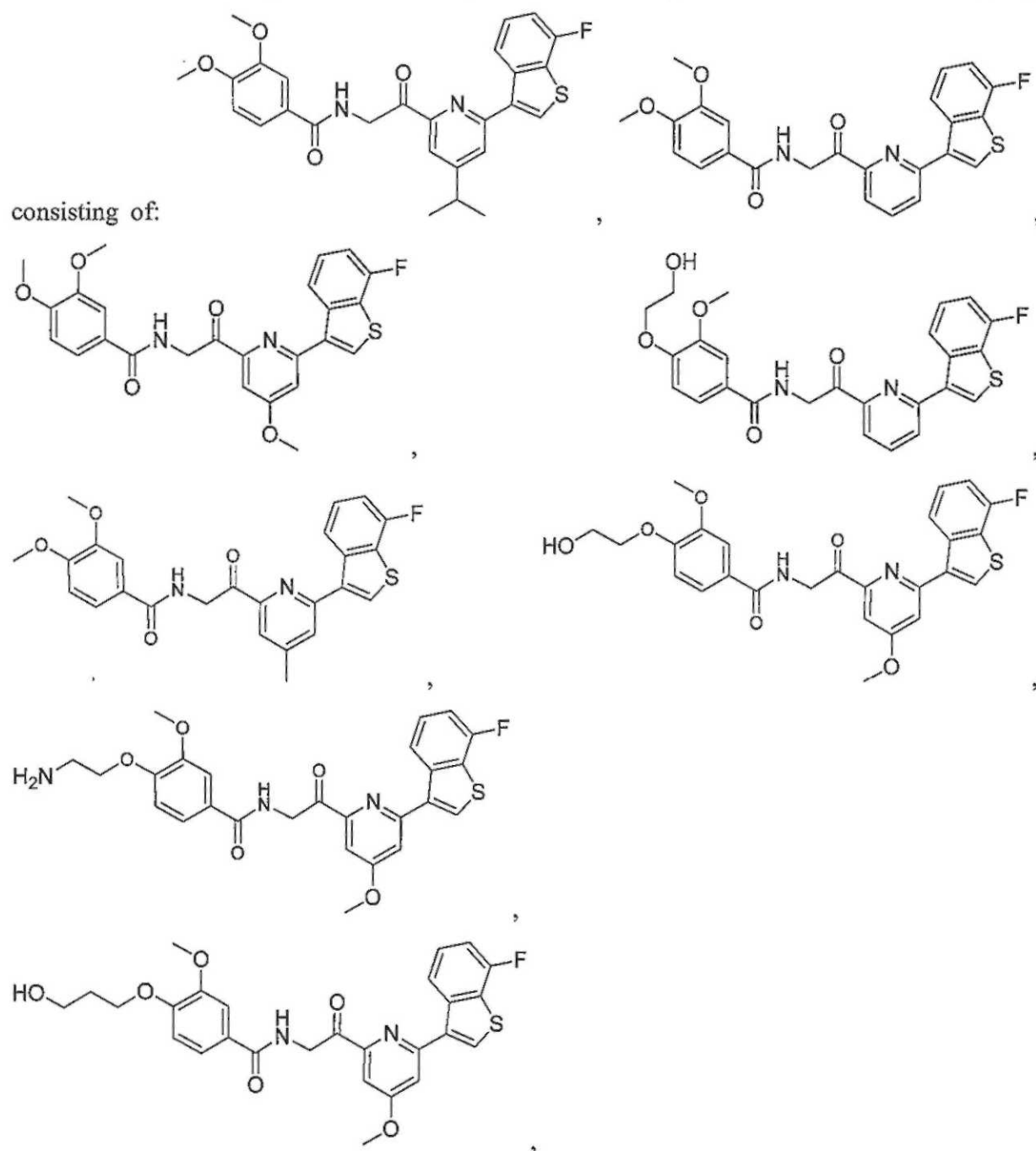
33. The compound of Claim 32, wherein the substituted benzothiophene is

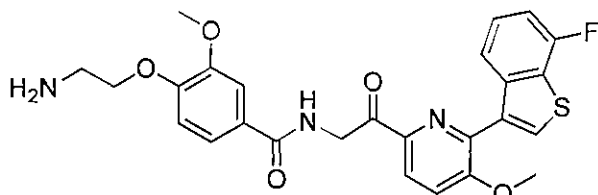
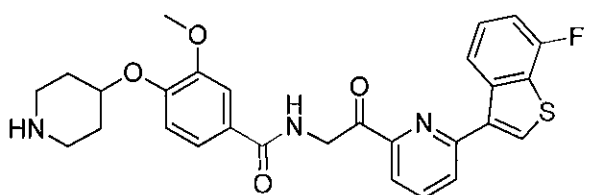
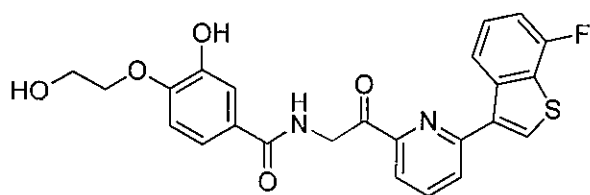
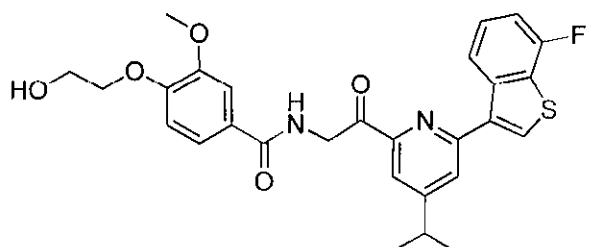
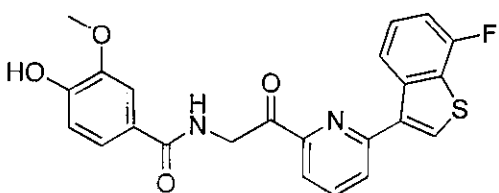
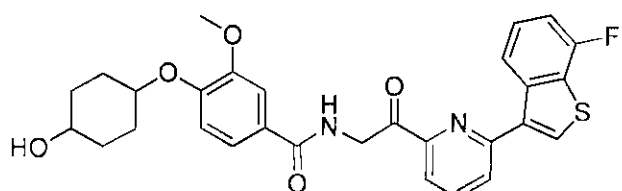
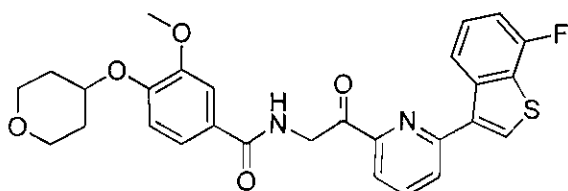
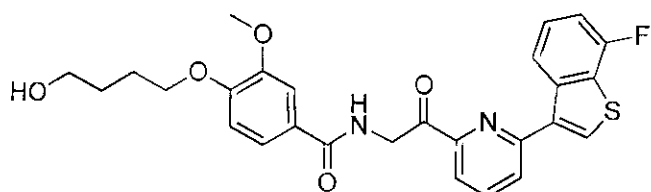
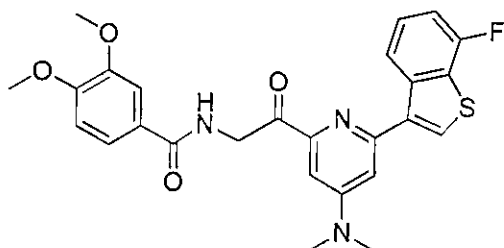
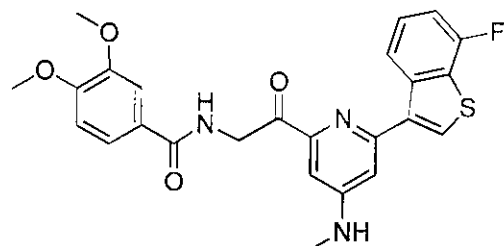
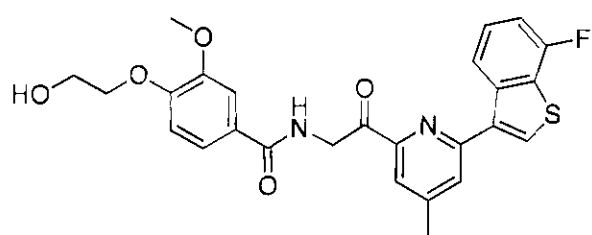


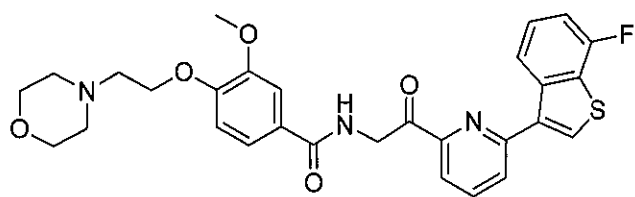
34. The compound of Claim 1, wherein the compound is selected from the group



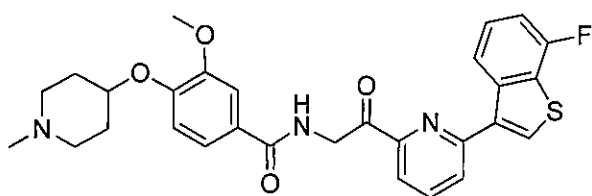
35. The compound of Claim 1, wherein the compound is selected from the group



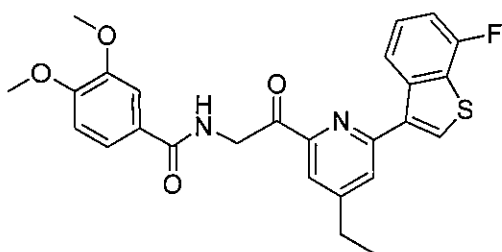




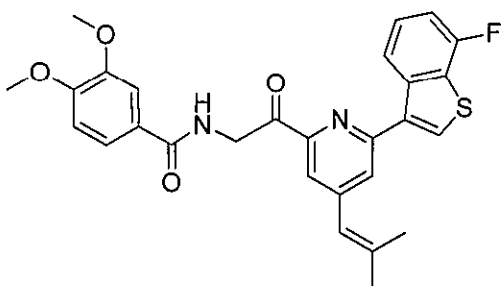
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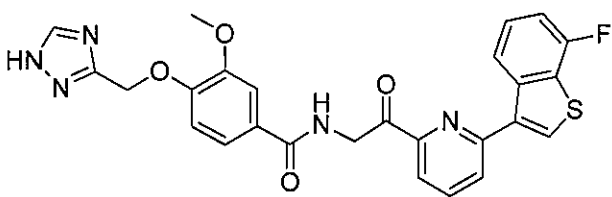
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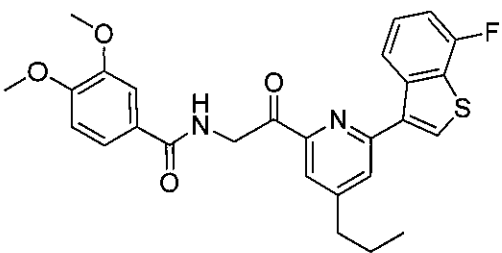
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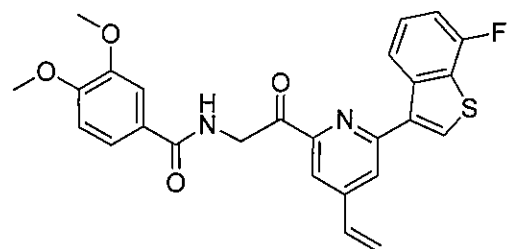
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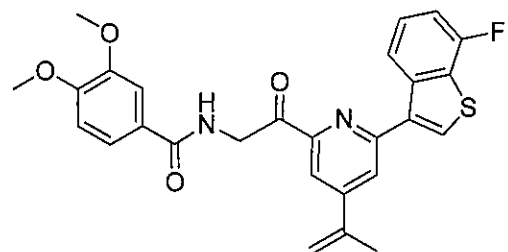
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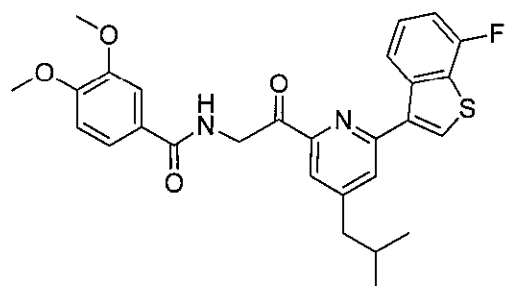
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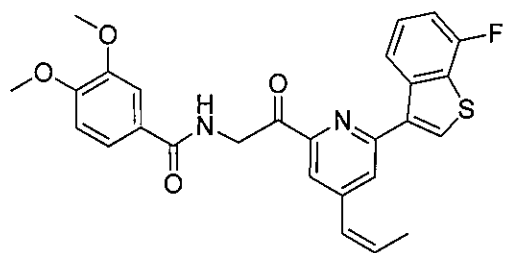
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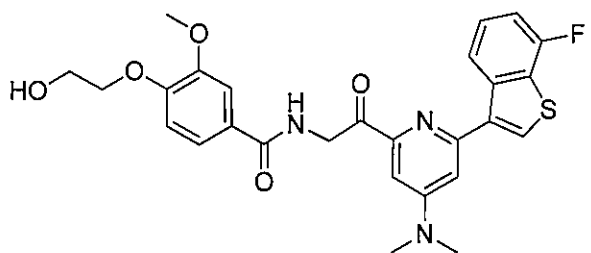
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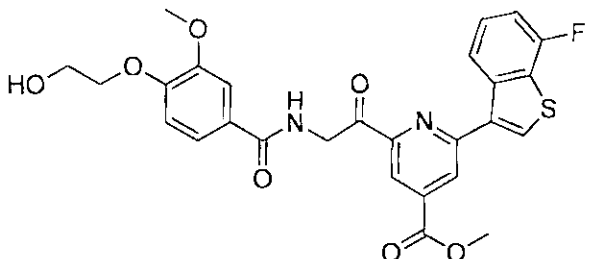
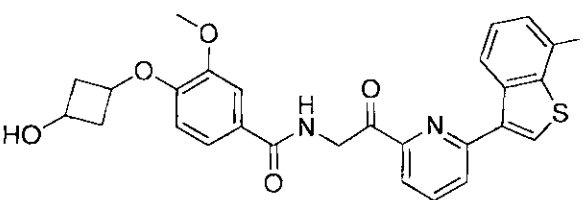
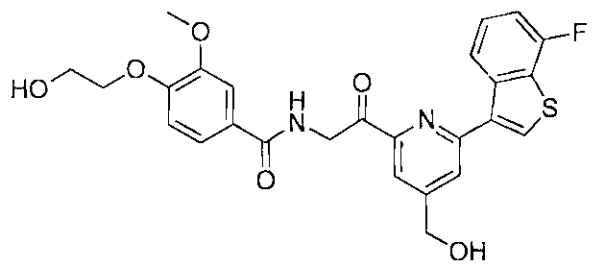
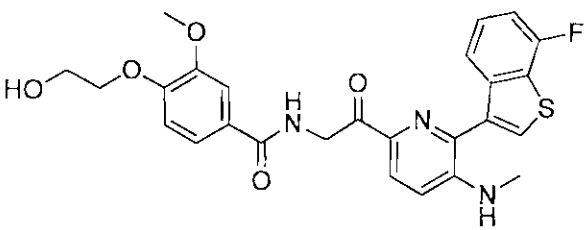
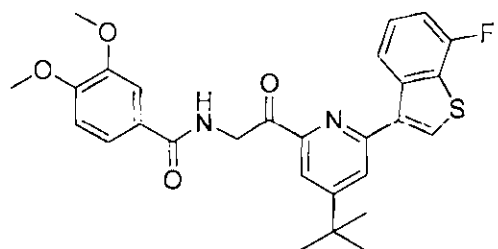
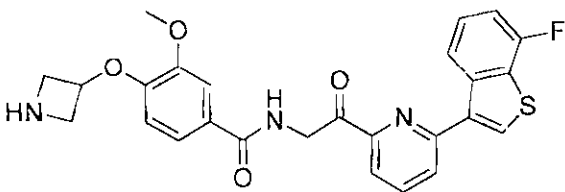
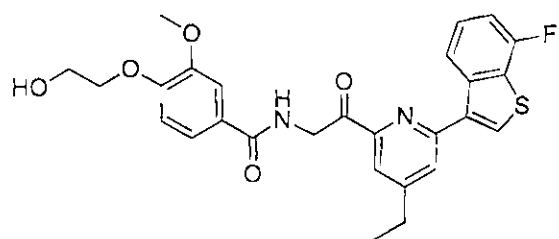
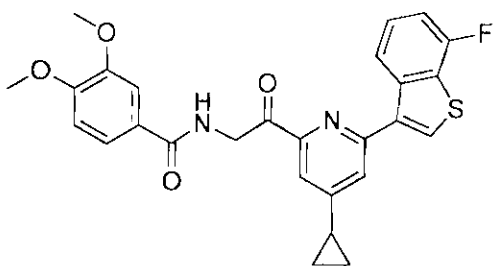
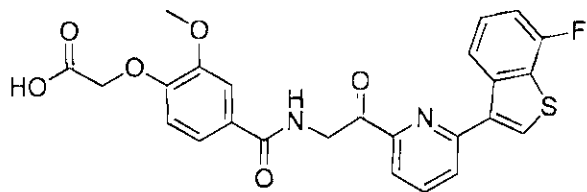
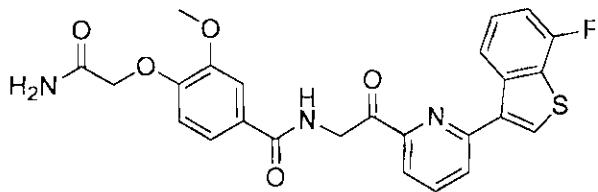
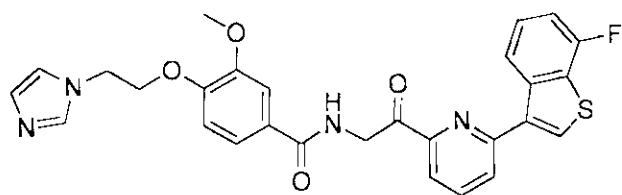
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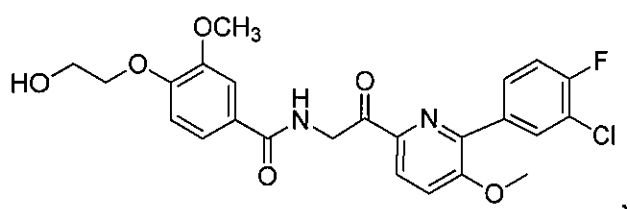
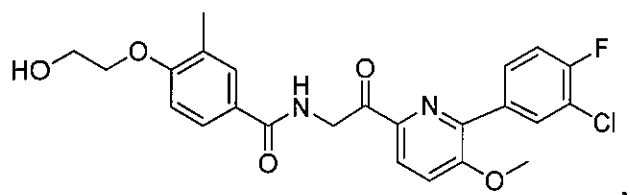
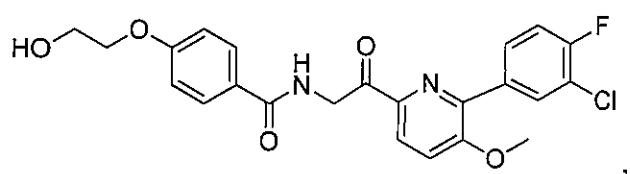
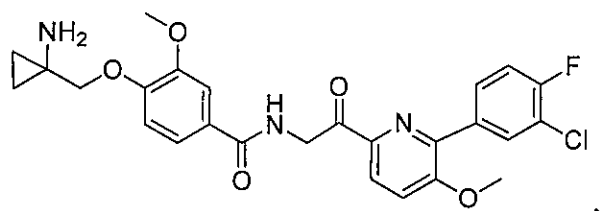
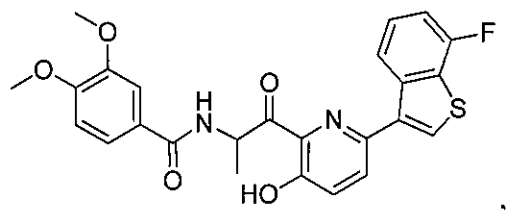
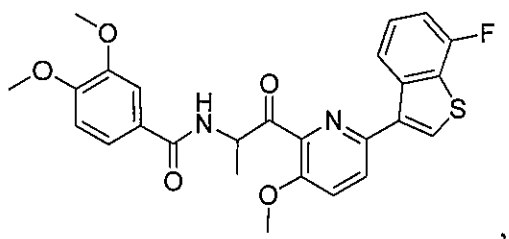
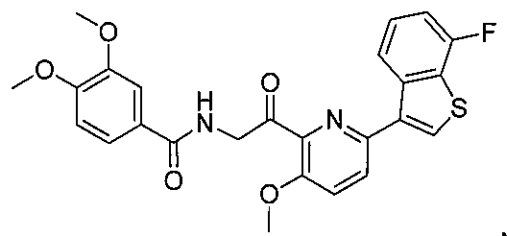
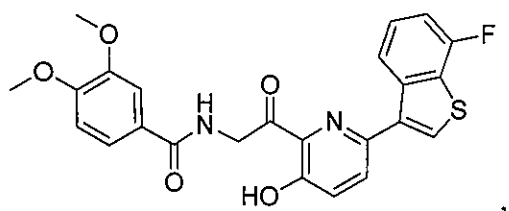
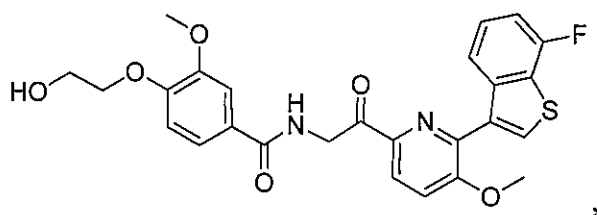
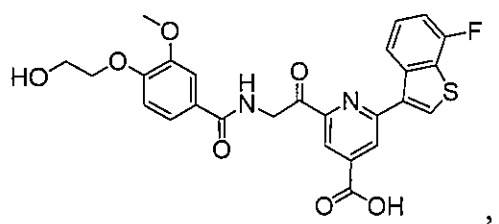


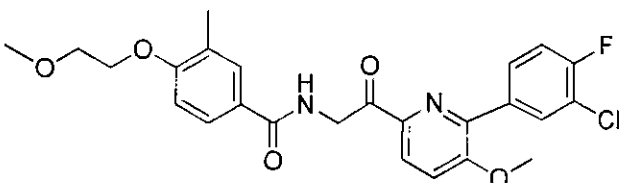
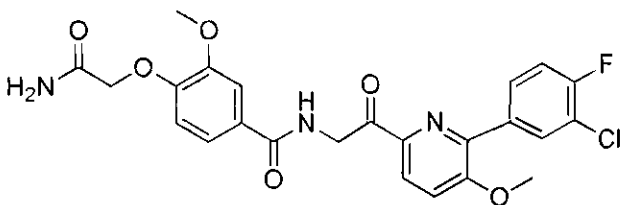
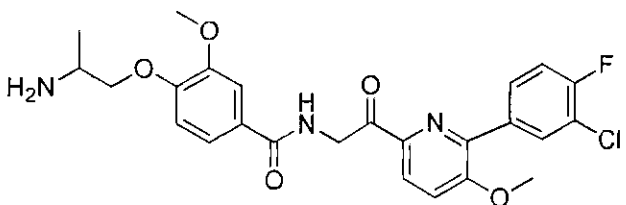
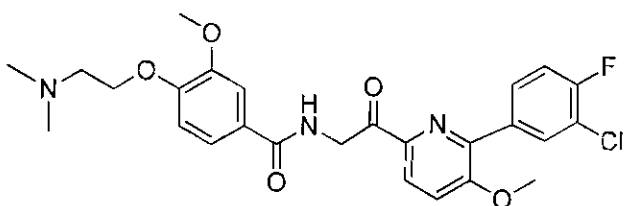
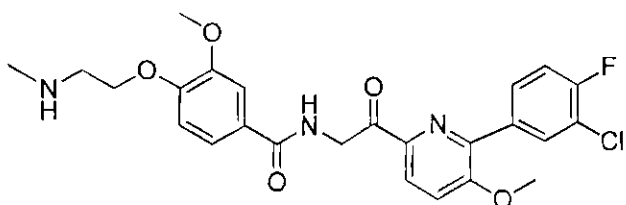
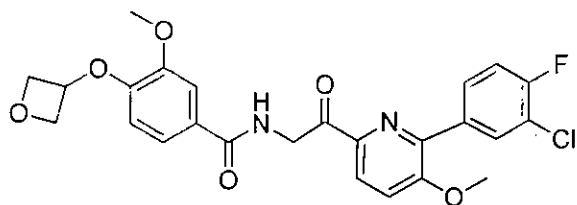
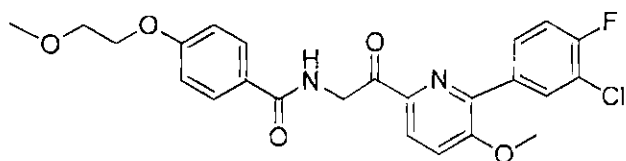
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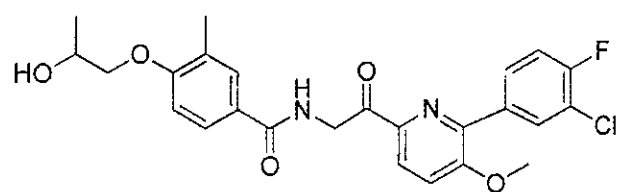


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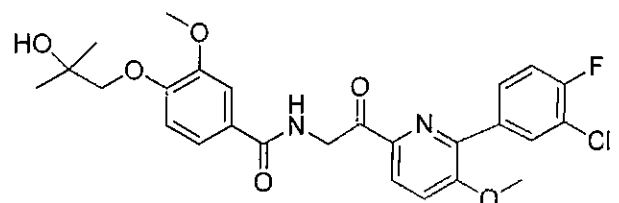




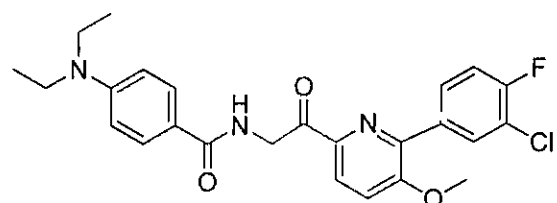




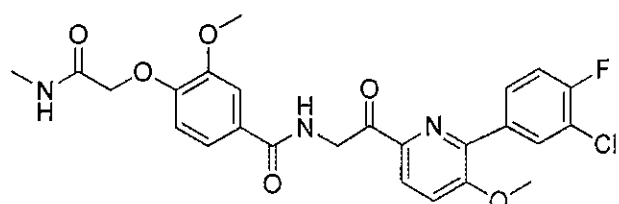
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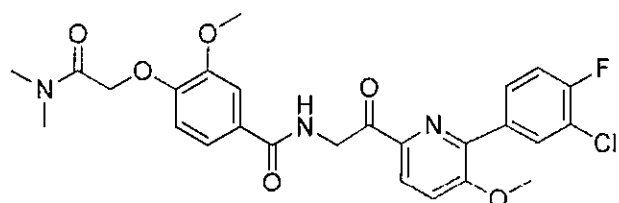
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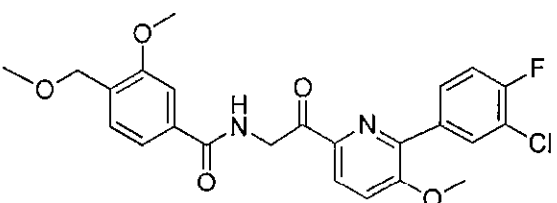
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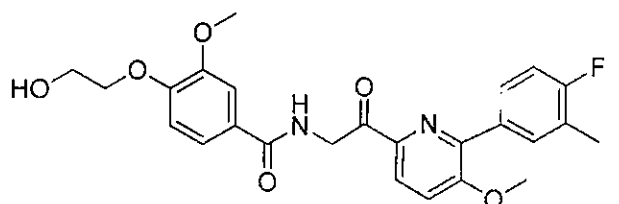
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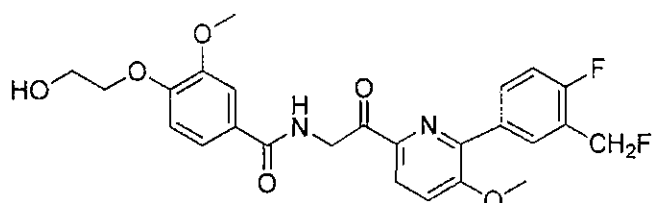
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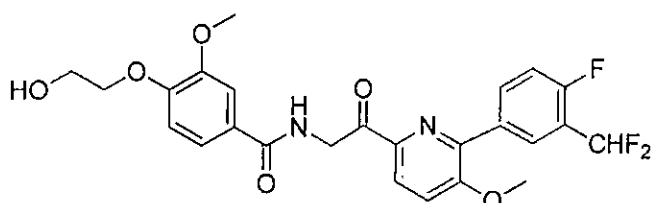
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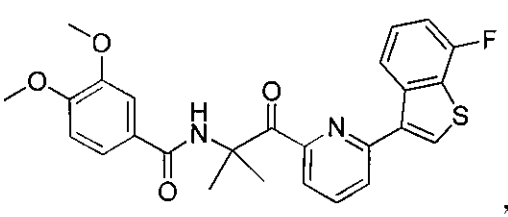
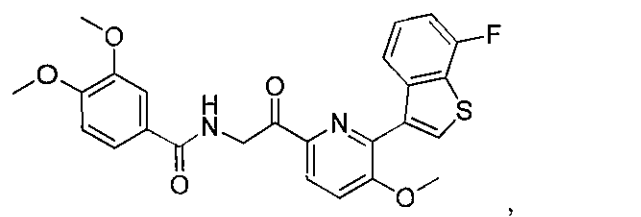
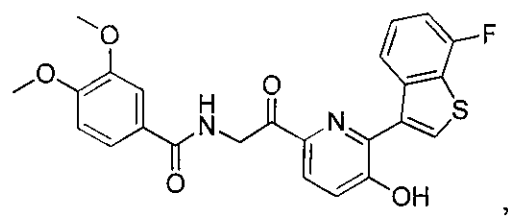
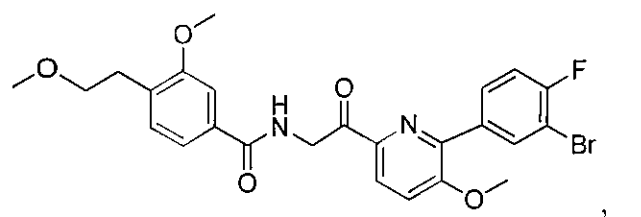
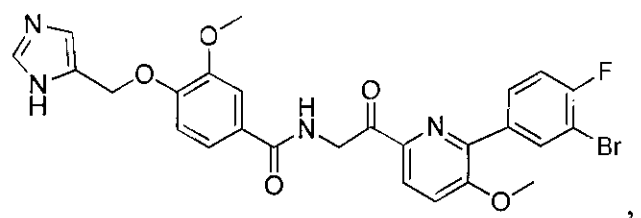
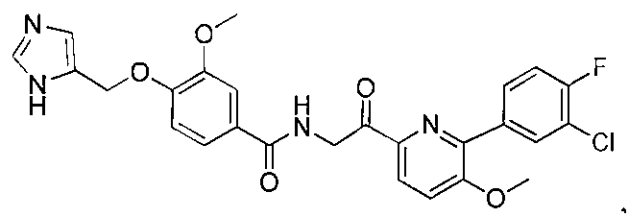
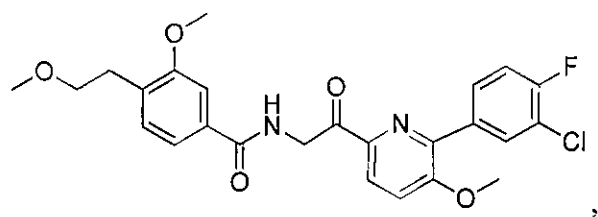
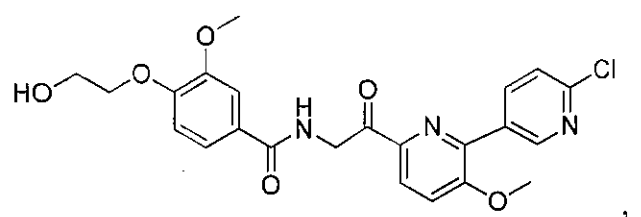
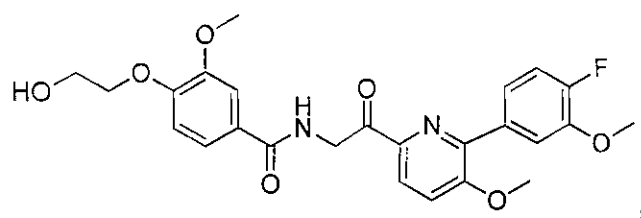
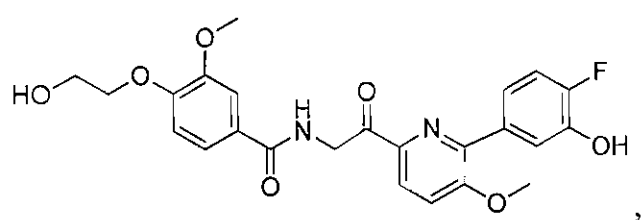
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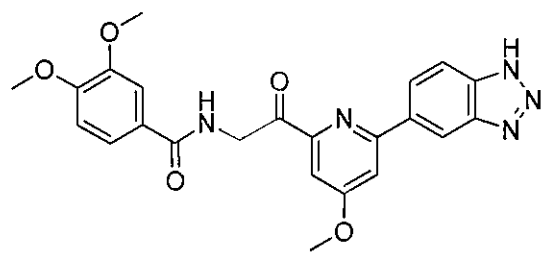
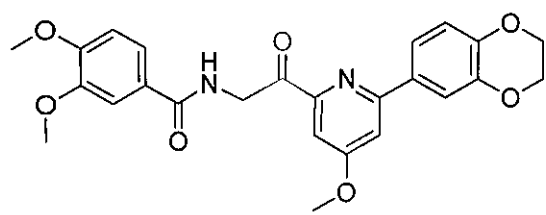
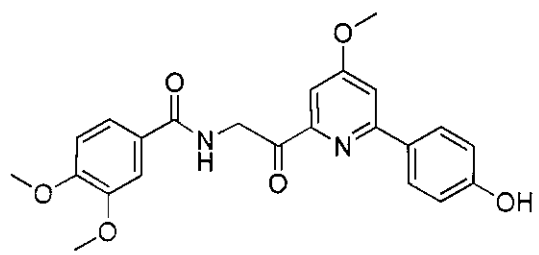
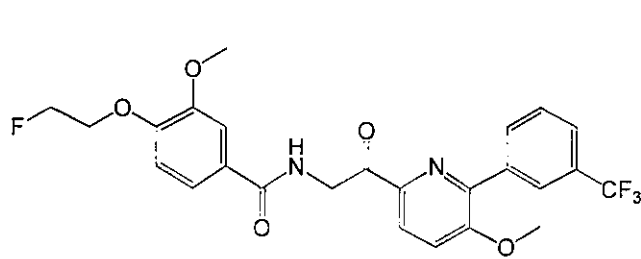
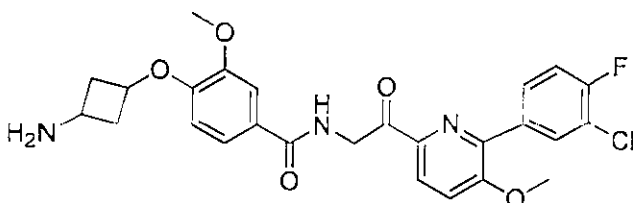
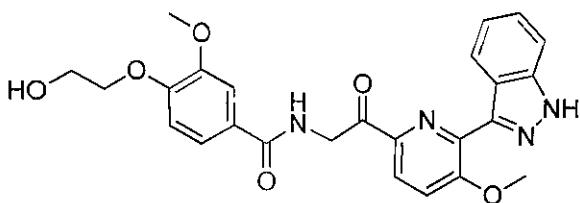
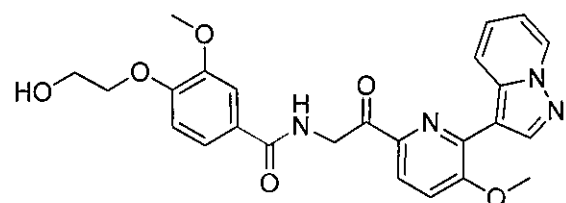
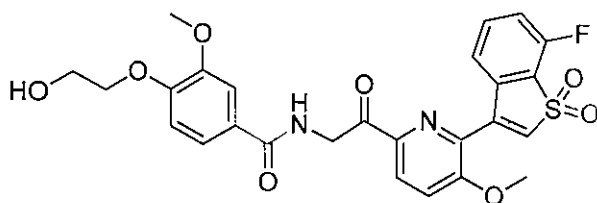
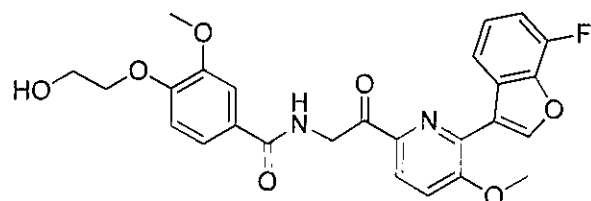
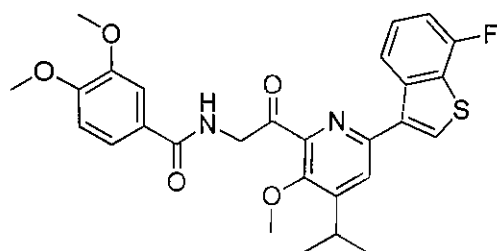


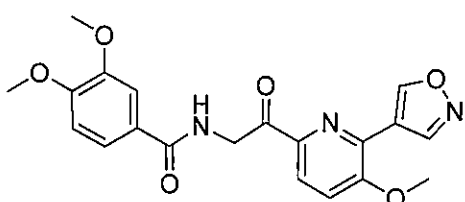
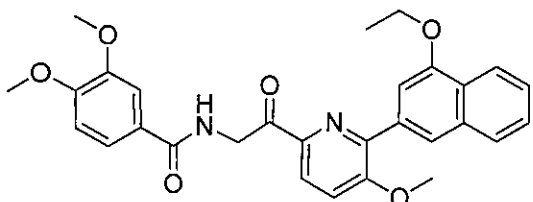
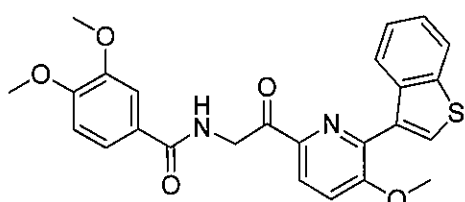
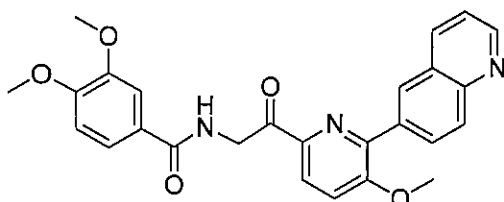
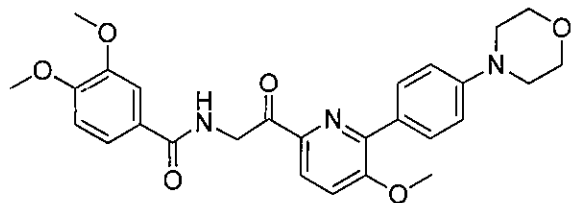
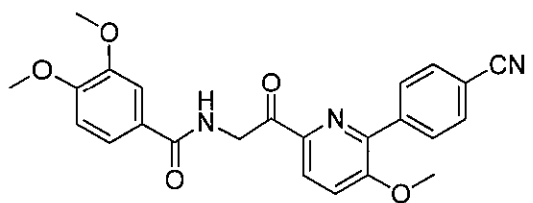
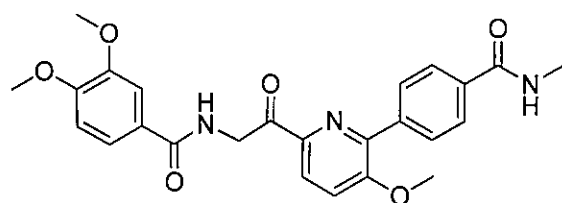
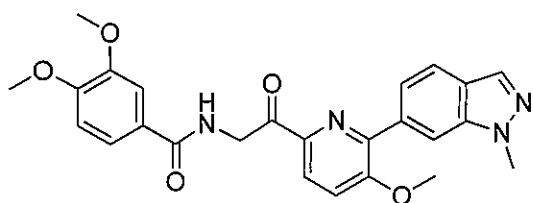
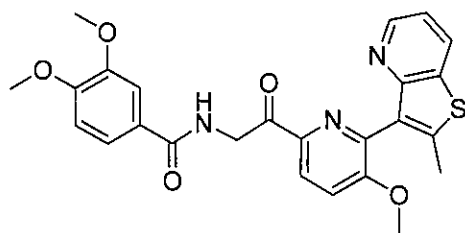
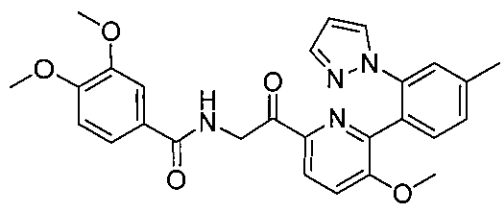
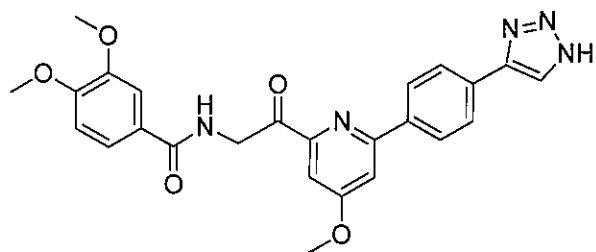
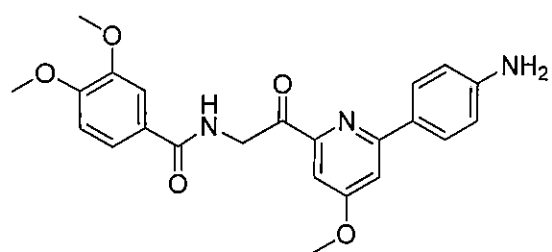
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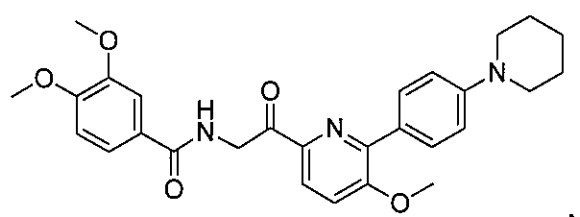
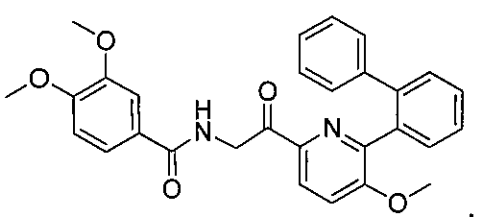
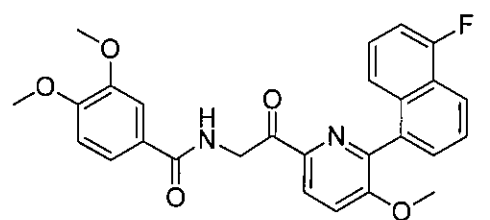
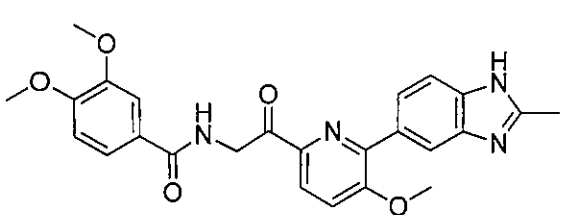
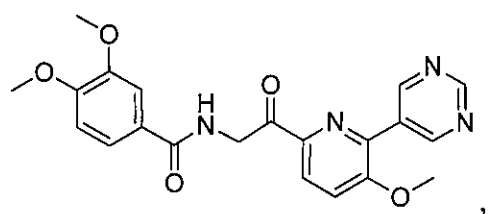
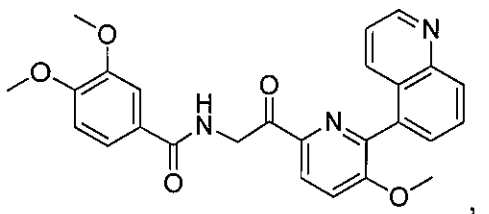
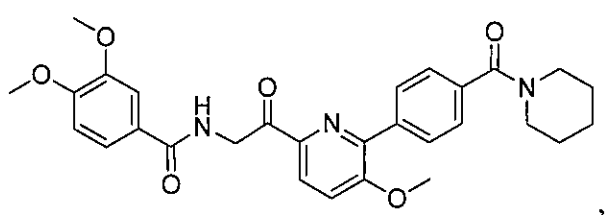
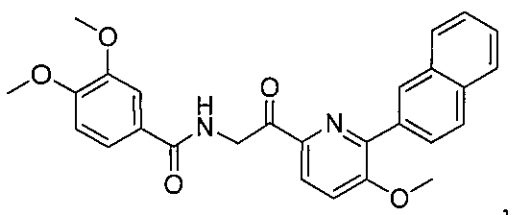
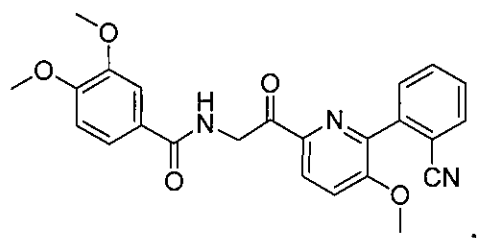
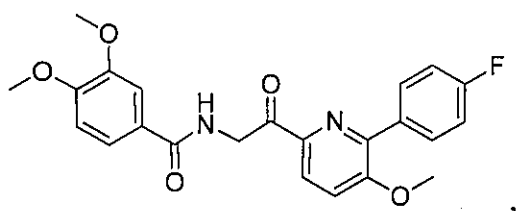
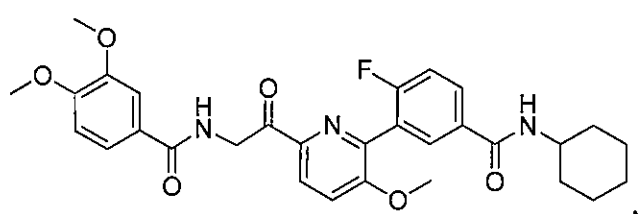
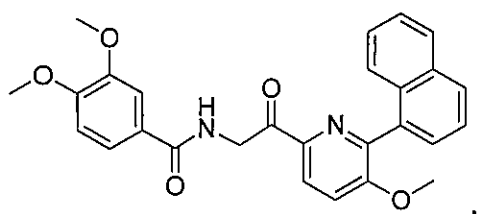
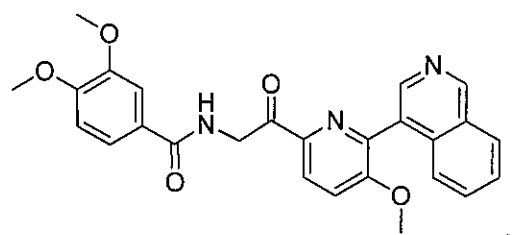
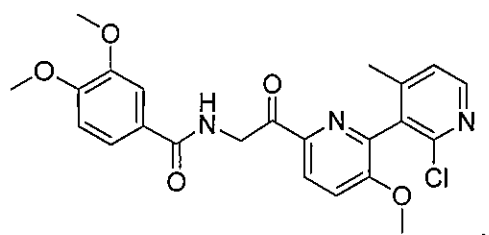


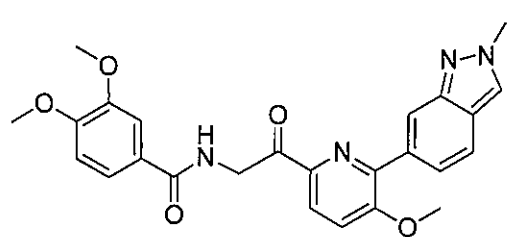
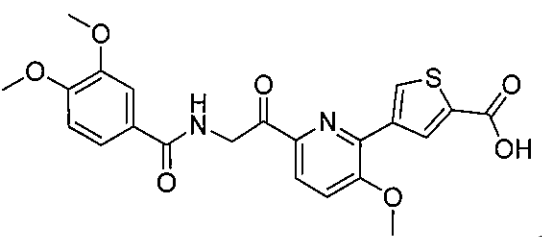
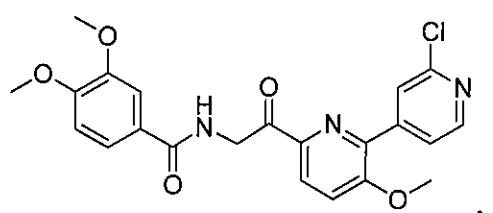
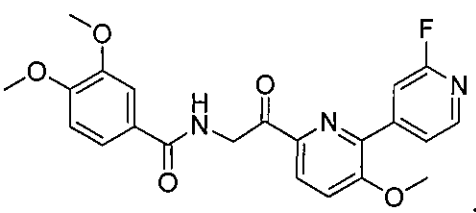
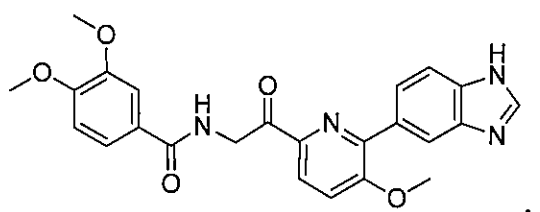
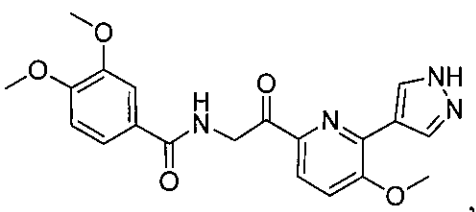
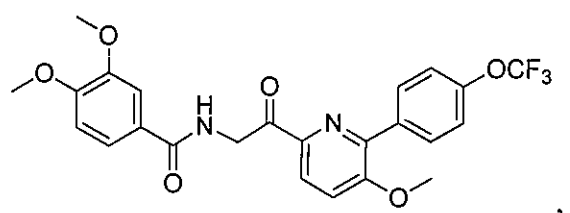
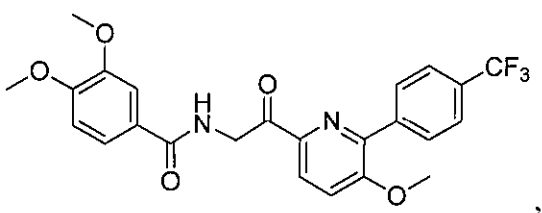
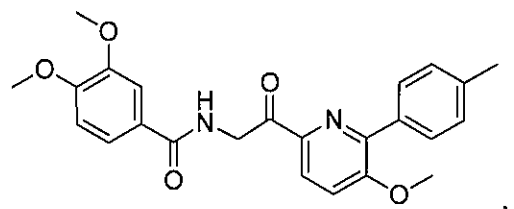
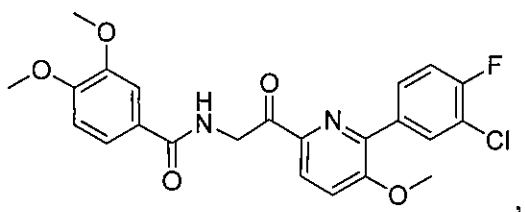
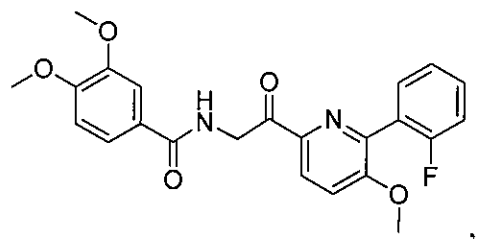
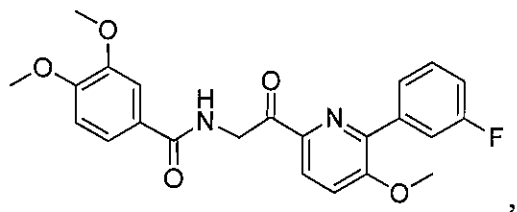
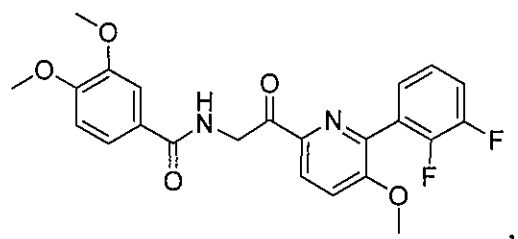
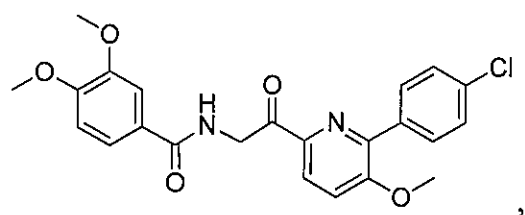
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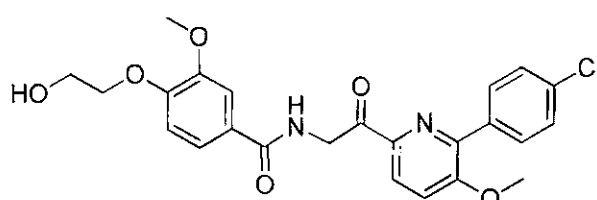
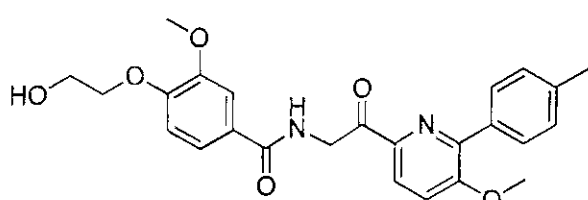
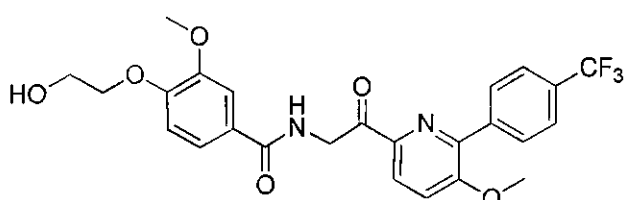
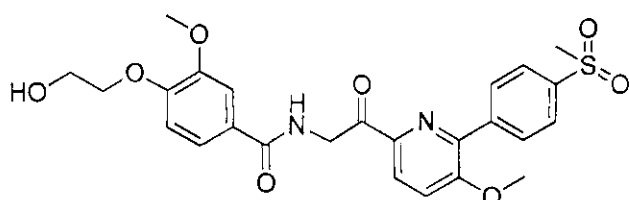
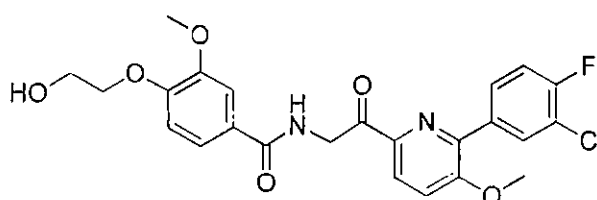
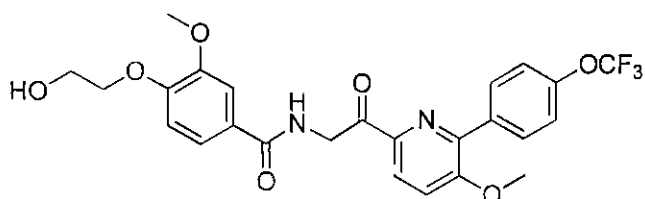
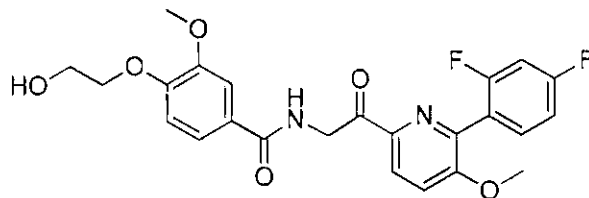
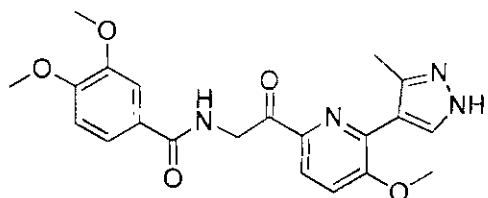
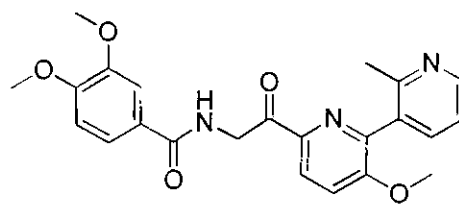
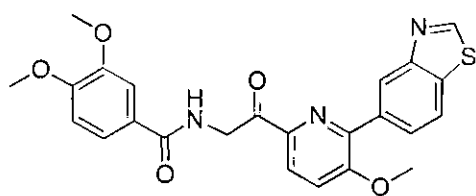


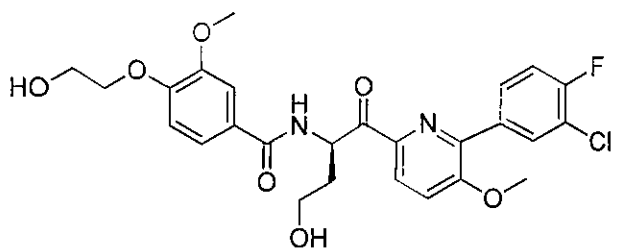
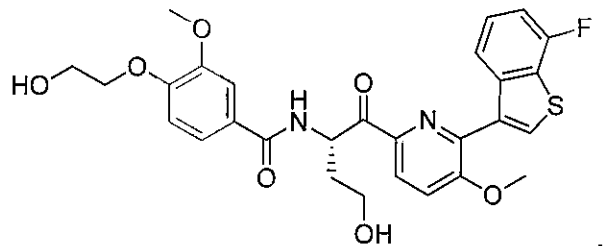
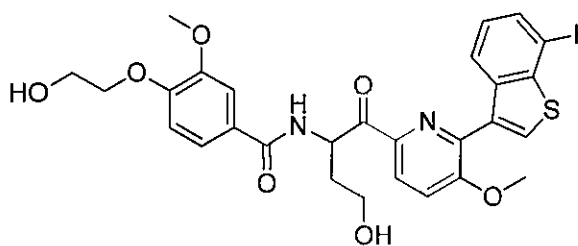
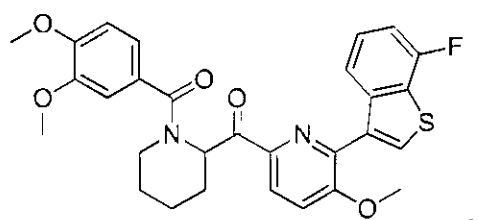
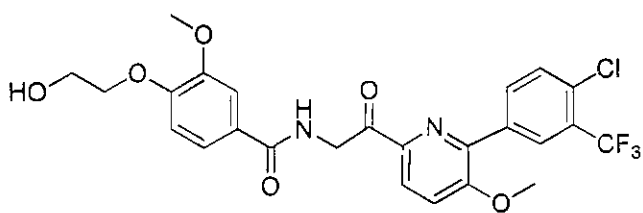
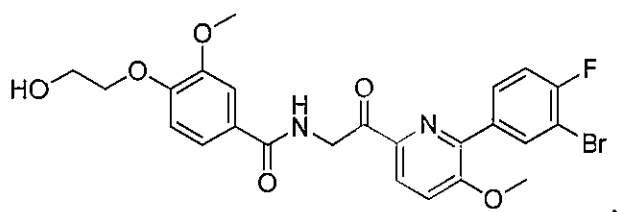
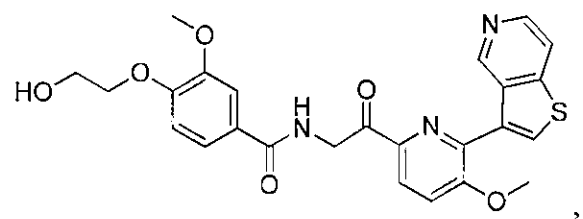
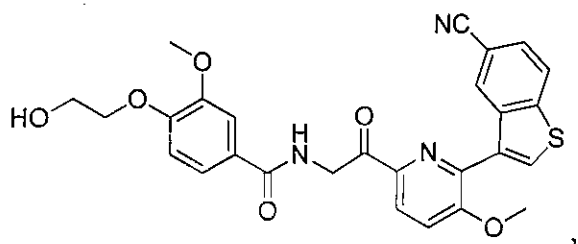
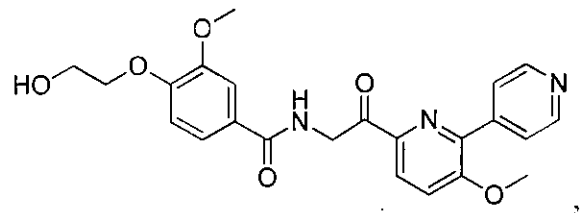
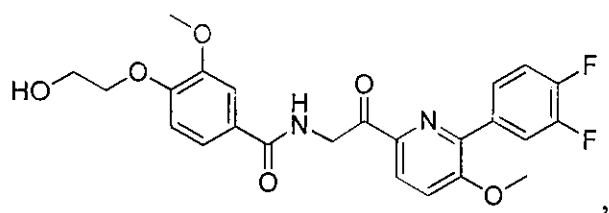


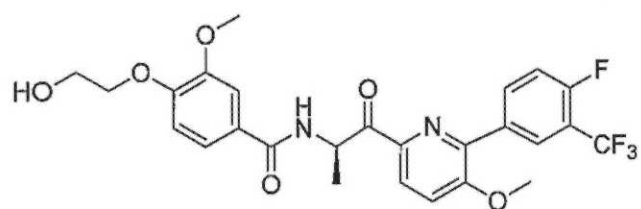
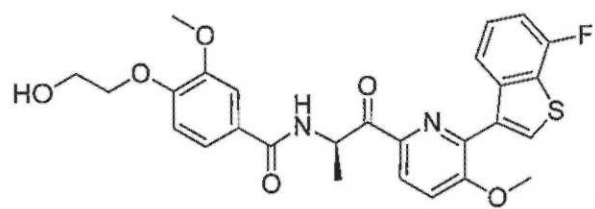
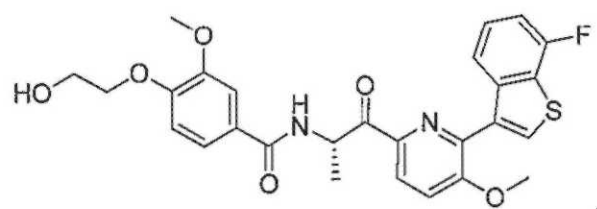
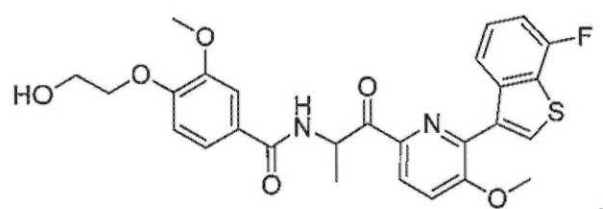
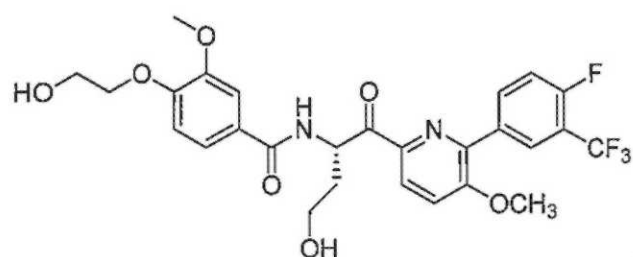
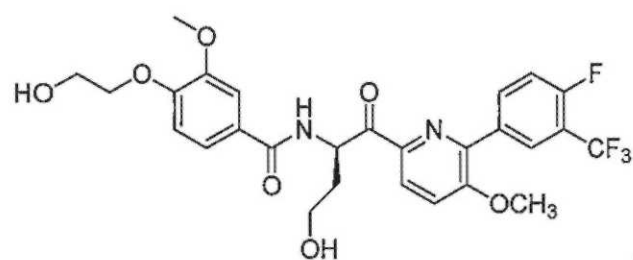
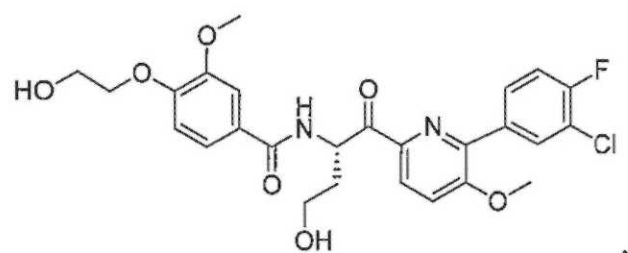


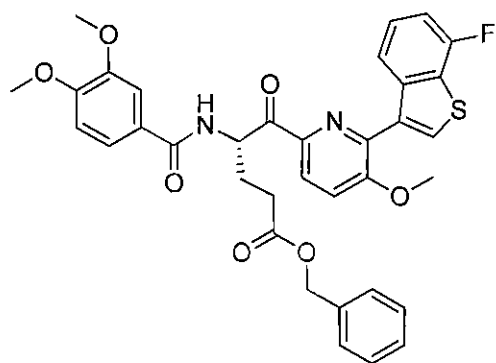
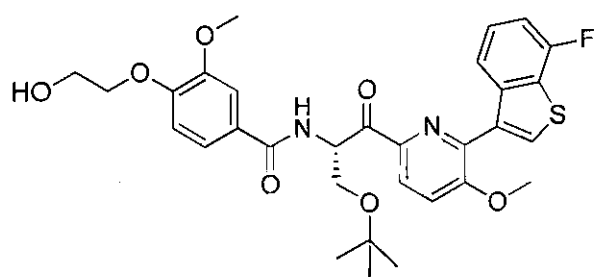
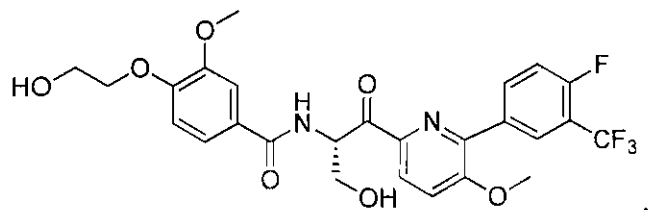
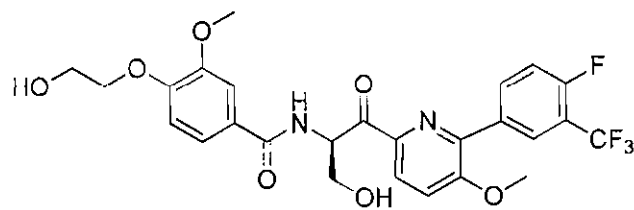
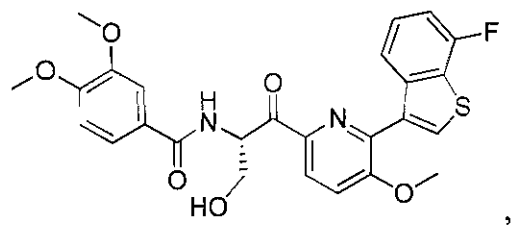
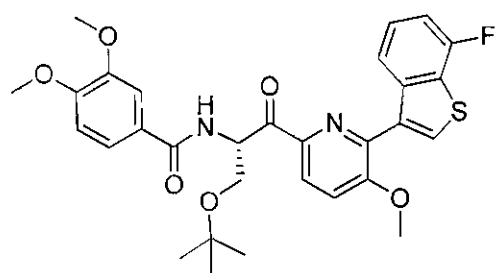
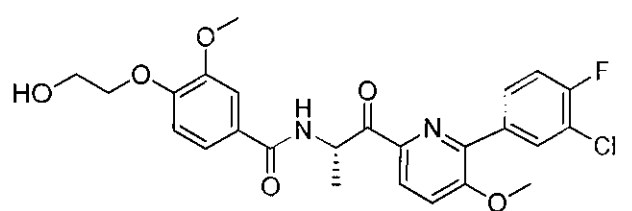
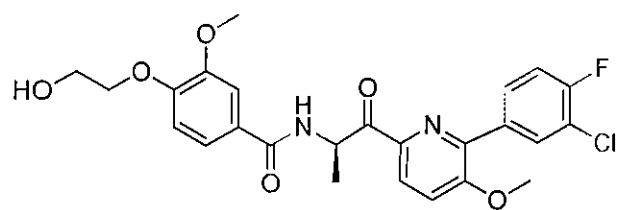
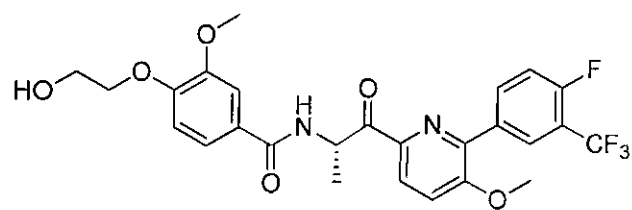


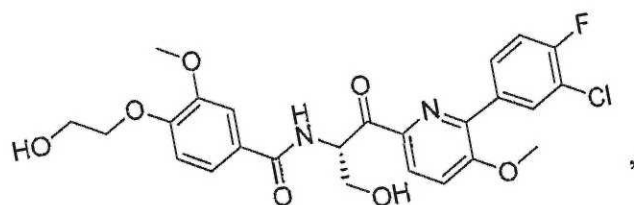
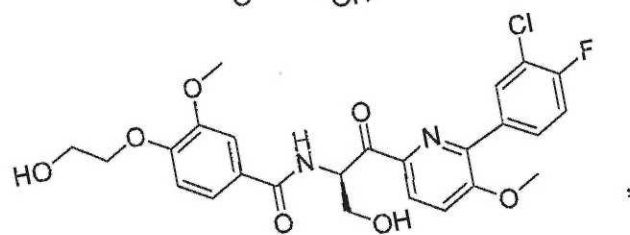
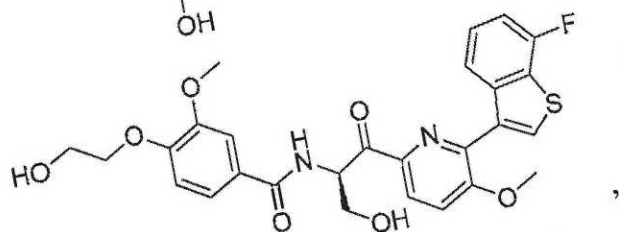
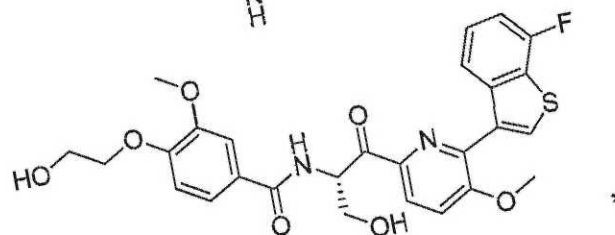
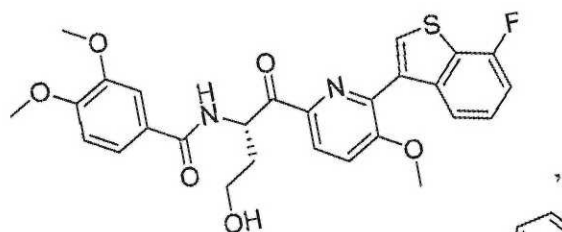
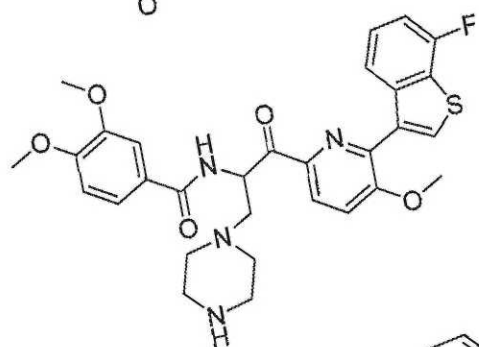
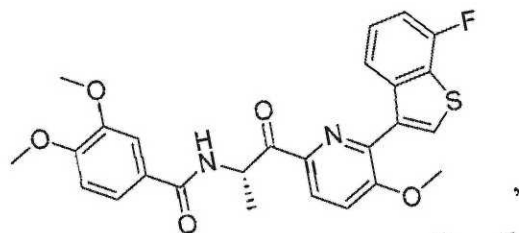
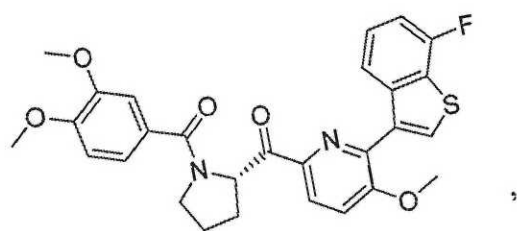
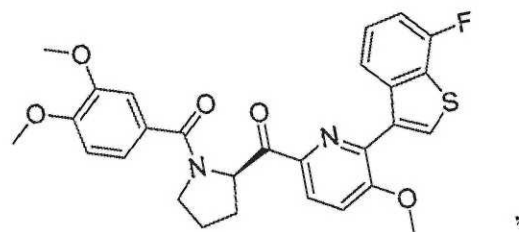
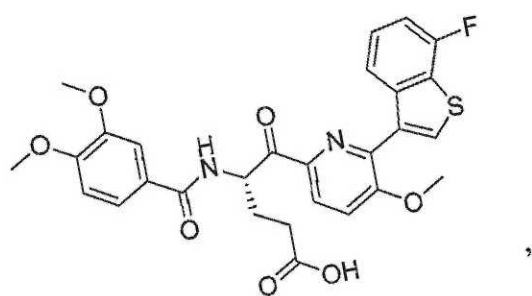


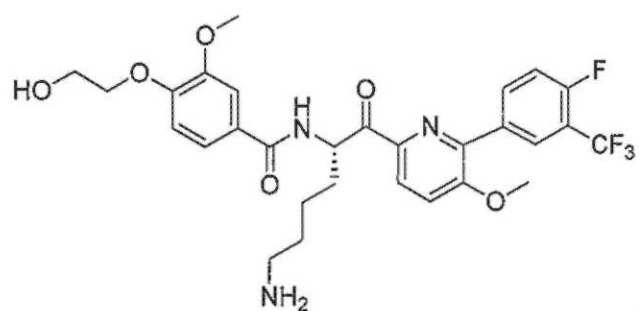




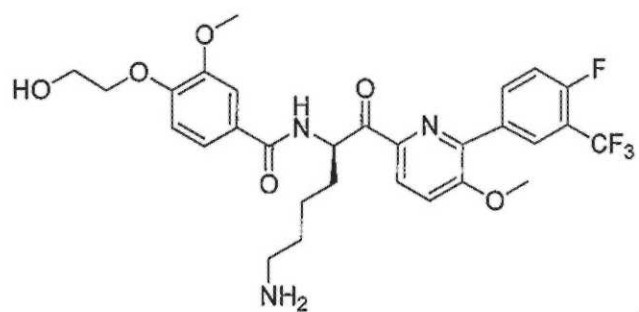




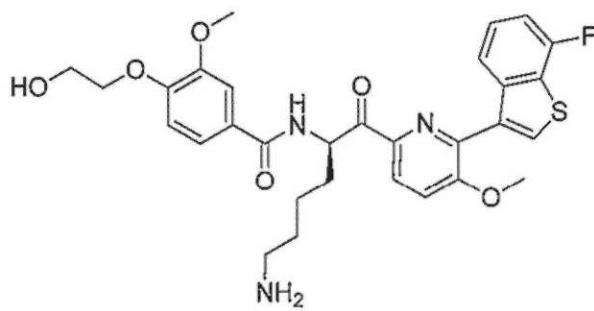
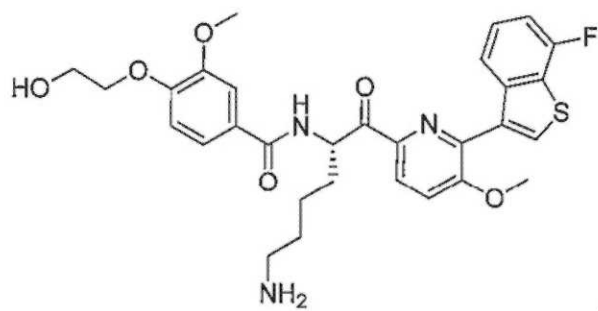




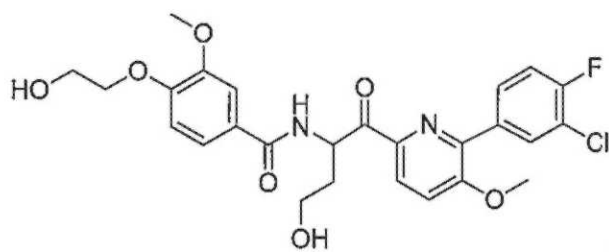
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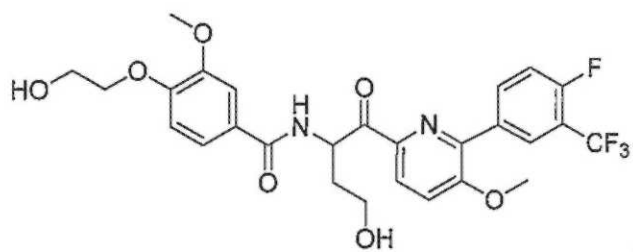
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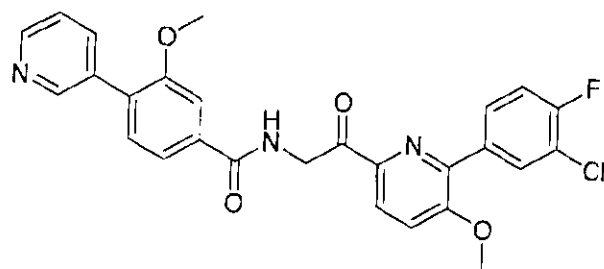
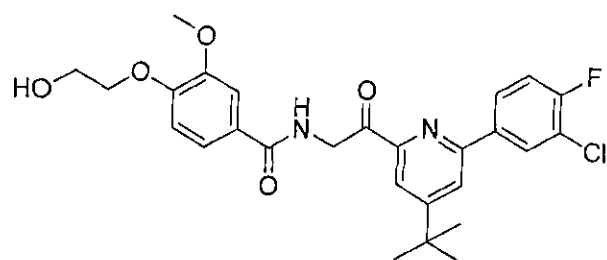
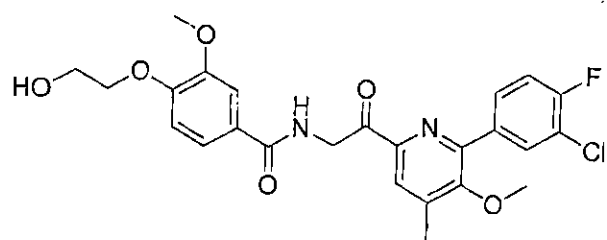
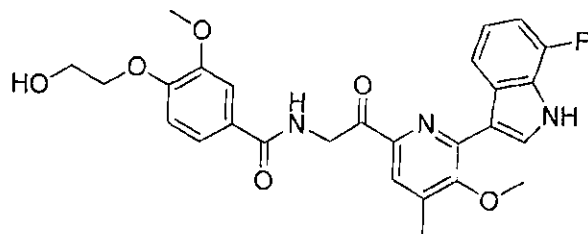
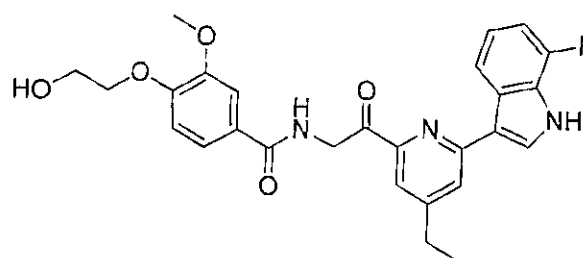
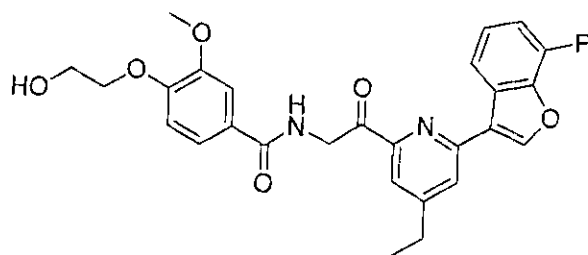
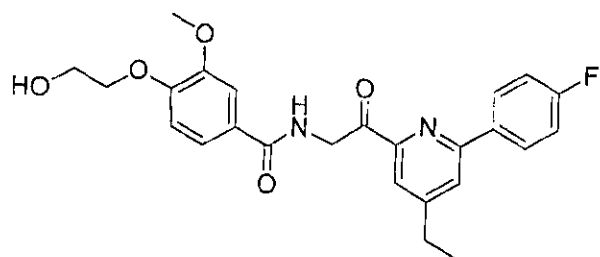
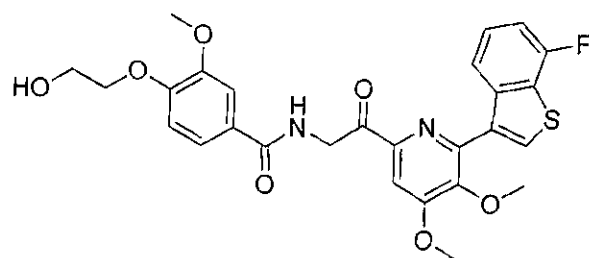
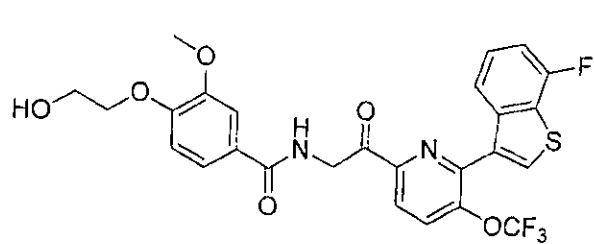
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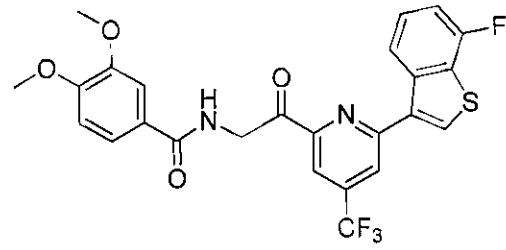
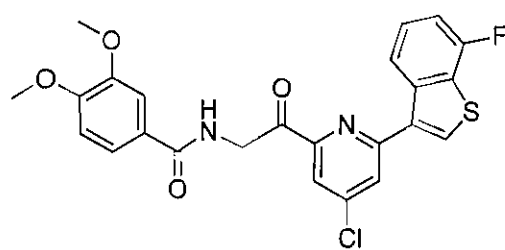
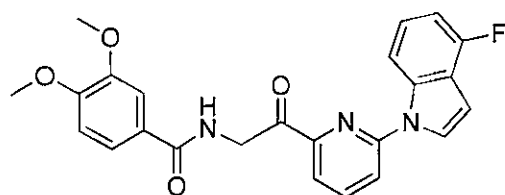
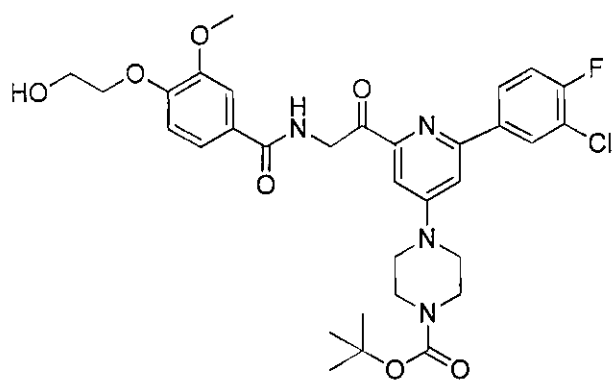
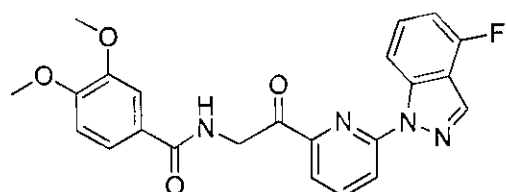
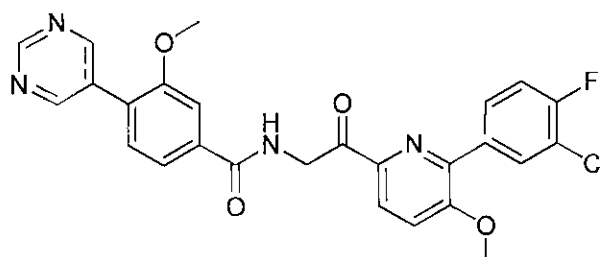
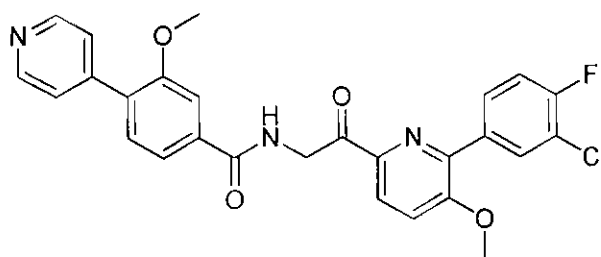
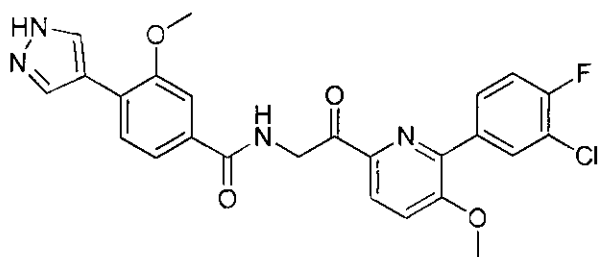


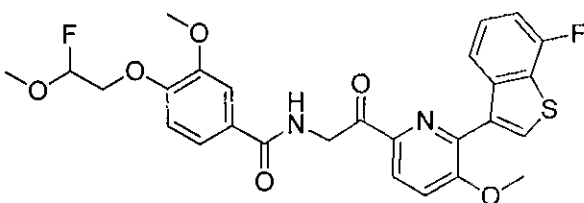
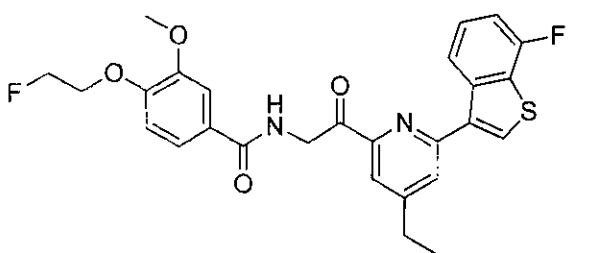
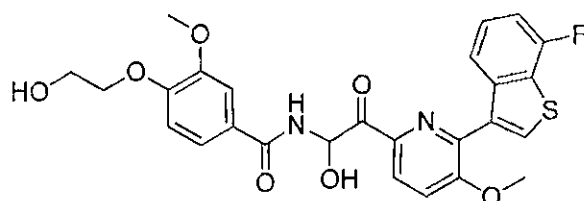
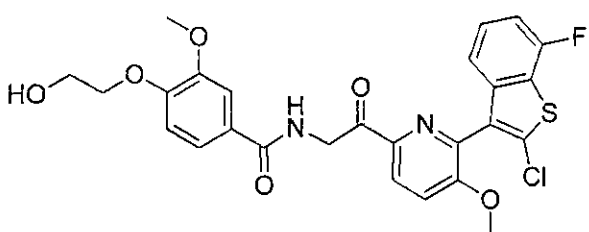
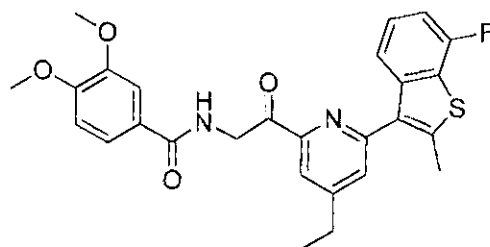
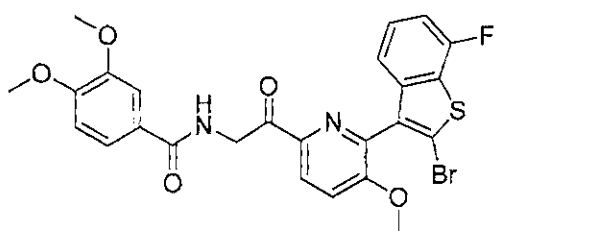
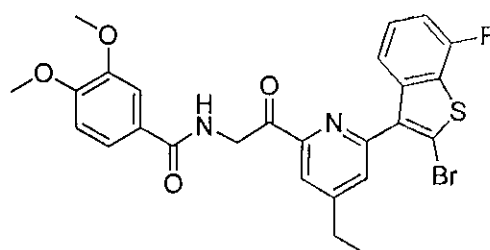
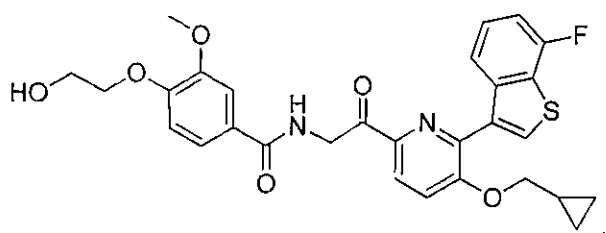
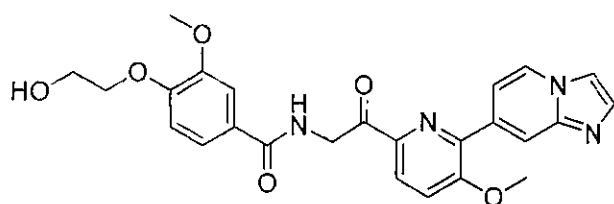
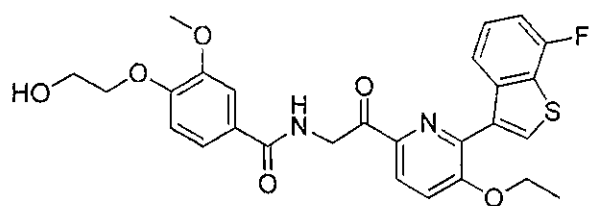
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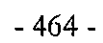


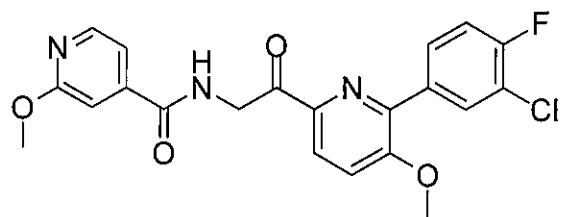
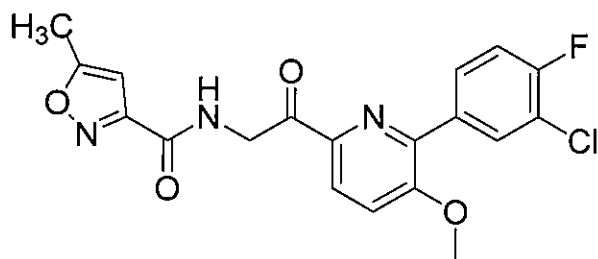
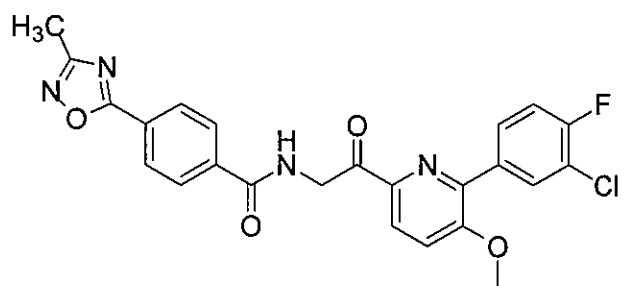
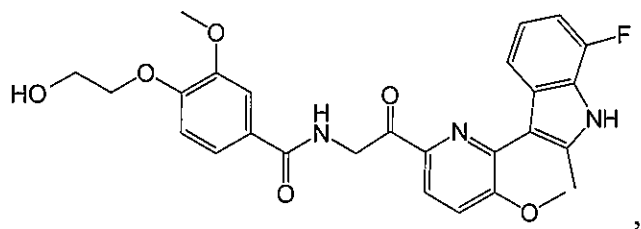
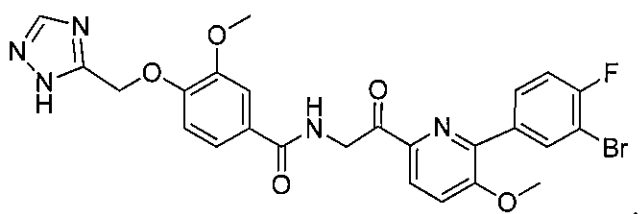
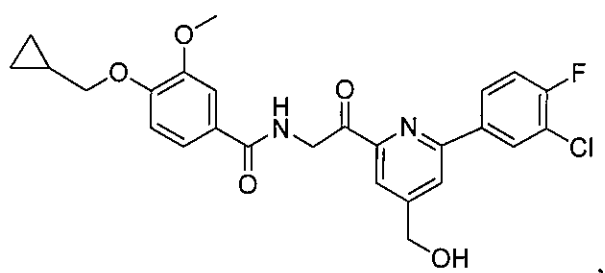
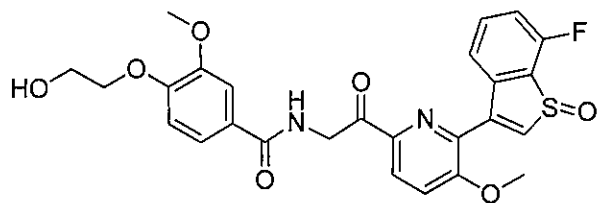
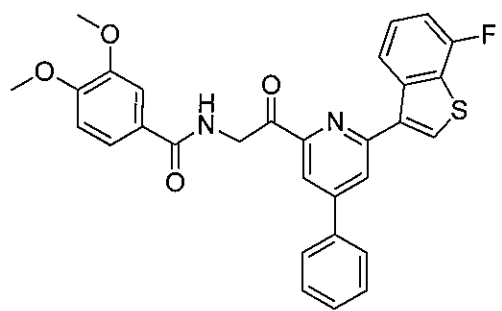
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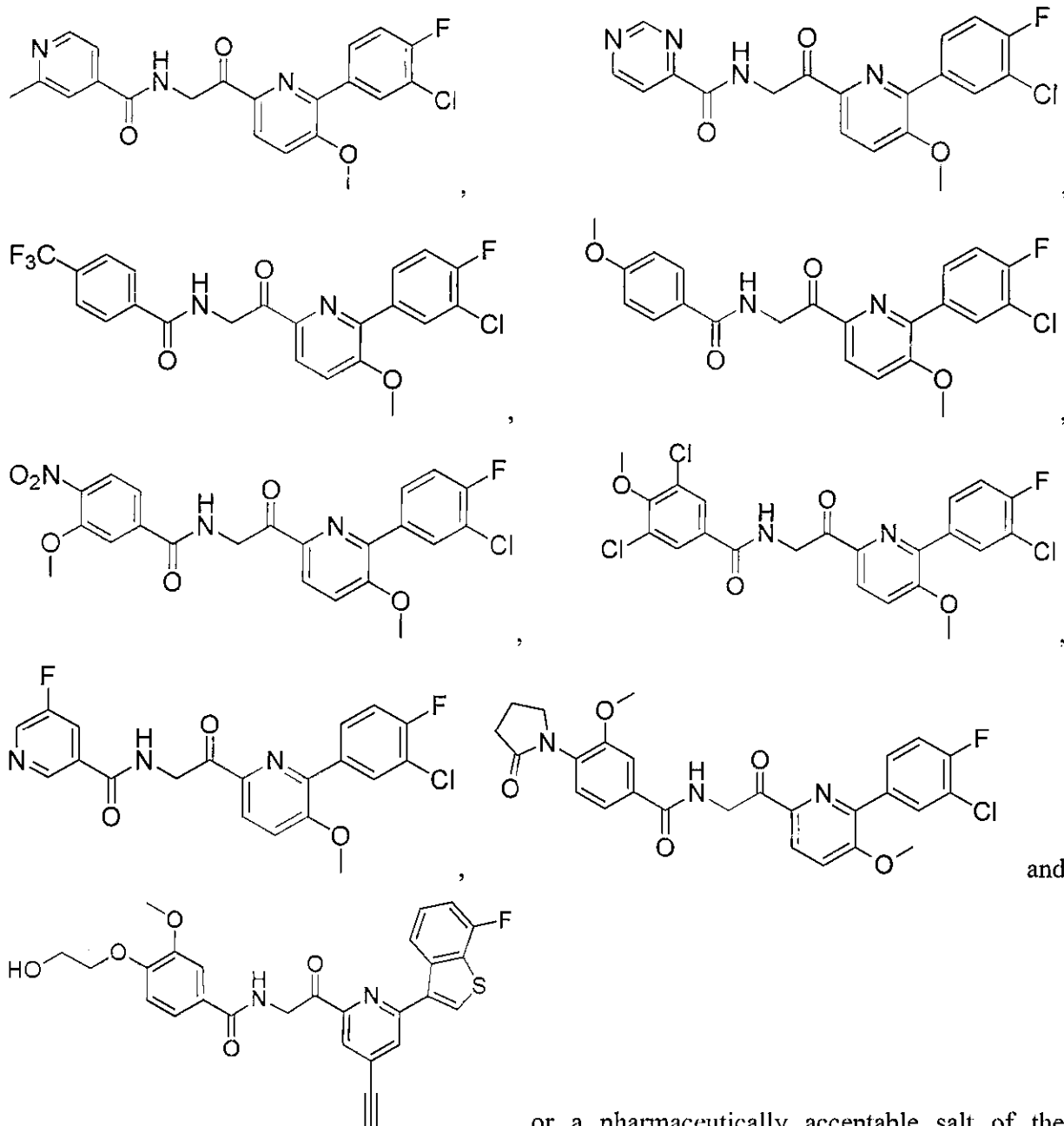












or a pharmaceutically acceptable salt of the foregoing.

36. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-35, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient, or combination thereof.

37. Use of an effective amount of a compound of any one of Claims 1-35, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for ameliorating or treating a paramyxovirus infection.

38. Use of an effective amount of a compound of any one of Claims 1-35, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting replication of a paramyxovirus.

39. The use of Claim 37 or 38, wherein the paramyxovirus is a human respiratory syncytial virus.

40. The use of Claim 37 or 38, wherein the paramyxovirus is a human respiratory syncytial virus, and further comprising the use of an effective amount of one or more anti RSV-agents.

41. The use of Claim 40, wherein the one or more anti-RSV agents is selected from the group consisting of ribavirin, palivizumab, RSV-IGIV, ALN-RSV01, BMS-433771, RFI-641, RSV604, MDT-637, BTA9881, TMC-353121, MBX-300 and YM-53403.