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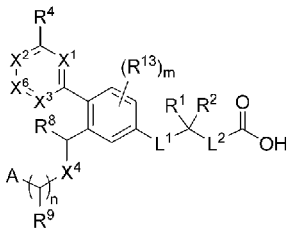
(54) Title: COMPOUNDS AND COMPOSITIONS FOR TREATING CONDITIONS ASSOCIATED WITH LPA RECEPTOR ACTIVITY



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(57) Abstract: The present disclosure provides LPA antagonists of formula I, as well as pharmaceutical compositions comprising the compounds disclosed herein. Also provided are methods for treating LPA-associated diseases, disorders, and conditions.

COMPOUNDS AND COMPOSITIONS FOR TREATING CONDITIONS ASSOCIATED WITH LPA RECEPTOR ACTIVITY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The application claims the benefit of International Patent Application Number PCT/CN2022/077844, filed on February 25, 2022, International Patent Application Number PCT/CN2022/094839, filed on May 25, 2022, and International Patent Application Number PCT/CN2022/117690, filed September 8, 2022, each of which is incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure provides LPA antagonists, as well as pharmaceutical compositions comprising the compounds disclosed herein. Also provided are methods for treating LPA-associated diseases, disorders, and conditions.

BACKGROUND

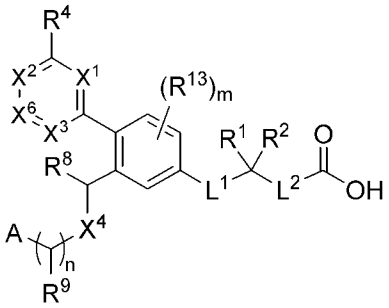
[0003] Various lipid mediators, including eicosanoid and platelet activating factor (PAF) are produced by the activity of phospholipase from cell membranes. Lysophospholipids are one class of these membrane-derived bioactive lipid mediators and include lysophosphatidic acid (LPA). LPA is not a single molecular entity but a collection of endogenous structural variants with fatty acids of varied lengths and degrees of saturation. LPAs affect cellular functions that include cellular proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis. These functions influence many biological processes that include neurogenesis, angiogenesis, wound healing, immunity, and carcinogenesis. LPA has a role as a biological effector molecule and has a diverse range of physiological actions such as, but not limited to, effects on blood pressure, platelet activation, and smooth muscle contraction, and a variety of cellular effects, which include cell growth, cell rounding, neurite retraction, and actin stress fiber formation and cell migration. The effects of LPA are predominantly receptor mediated. Activation of the LPA receptors (LPA_1, LPA_2, LPA_3, LPA_4, LPA_5, LPA_6) with LPA mediates a range of downstream signaling cascades.

SUMMARY

[0004] Antagonizing LPA receptors (such as the LPA_1 receptor) may be useful for the treatment of a variety of disorders, including fibrosis such as pulmonary fibrosis, hepatic fibrosis, renal fibrosis, arterial fibrosis and systemic sclerosis, and thus the diseases that result from fibrosis (e.g., pulmonary fibrosis, for

example, Idiopathic Pulmonary Fibrosis (IPF), hepatic fibrosis, including Non-alcoholic Steatohepatitis (NASH), renal fibrosis, such as diabetic nephropathy, systemic sclerosis-scleroderma, etc.), COVID-19, chronic obstructive pulmonary disease (COPD), neuroinflammation, or multiple sclerosis. The present application describes LPA antagonists, as well as pharmaceutical compositions comprising the compounds disclosed herein. Also provided are methods for treating LPA-associated diseases, disorders, and conditions.

[0005] The present disclosure, in one embodiment, provides compounds of Formula I:



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or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of A is independently optionally substituted with one to five Z^1;

L^1 is a bond, -O-, -S-, -S(O)-, -S(O)$_2$-, -NR^{10}-, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^1 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

L^2 is a bond, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^2 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

X^1 is N or CR^3;

X^2 is N or CR^5;

X^3 is N or CR^7;

X^4 is O or CHR^{11}; provided that when A is C_{1-6} alkyl, then X^4 is O;

X^6 is N or CR^6;

n is 0, 1, or 2;

m is 0, 1, 2, or 3;

R^1 and R^2 are each independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl of R^1 and R^2 are independently optionally substituted with one to five Z^1;

or R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-10} cycloalkyl or heterocyclyl; wherein the C_{3-10} cycloalkyl or heterocyclyl is optionally substituted by one to five Z^1;

R^3 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^3 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^4 is halo, cyano, nitro, -OR^{14}, -N(R^{14})$_2$, -SR^{14}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^4 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, C_{1-5} alkoxy, and cyano;

or R^3 and R^4 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^5 is hydrogen, halo, cyano, nitro, -OR^{15}, -N(R^{15})$_2$, -SR^{15}, -C(O)R^{15}, -C(O)OR^{15}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl of R^5 is independently optionally substituted with one to five Z^1;

R^6 is hydrogen, halo, cyano, nitro, -OR^{16}, -N(R^{16})$_2$, -SR^{16}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^6 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^7 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5}

cycloalkyl, or 3-5 membered heterocyclyl of R^7 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

or R^6 and R^7 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^8 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^9 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^{10} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{10} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{11} is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

each R^{13} is independently hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl of R^{13} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{14} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{14} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{15} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{15} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{16} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{16} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

each Z^1 is independently halo, cyano, nitro, oxo, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-H, -L-C_{1-9} alkyl, -L-C_{2-9} alkenyl, -L-C_{2-9} alkynyl,

-L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^1 is independently optionally substituted with one to five Z^{1a};

each L is independently -O-, -S-, -NR^{20}-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NR^{20}-, -NR^{20}C(O)-, -OC(O)NR^{20}-, -NR^{20}C(O)O-, -NR^{20}C(O)NR^{21}-, -S(O)-, -$S(O)_2$-, -S(O)NR^{20}-, -$S(O)_2NR^{20}$-, -NR^{20}S(O)-, -$NR^{20}S(O)_2$-, -NR^{20}S(O)NR^{21}-, or -$NR^{20}S(O)_2NR^{21}$-;

each R^{20} and R^{21} is independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{20} and R^{21} is independently optionally substituted with one to five Z^{1a}; or an R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to five Z^{1a}; and

each Z^{1a} is independently halo, hydroxy, cyano, nitro, oxo, -SH, -NH_2, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1a} is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

[0006] Also provided herein are pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, and a pharmaceutically acceptable excipient.

[0007] Also provided herein are methods for treating or preventing an LPA-associated disease in a subject in need thereof, the method comprising administering to subject a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition thereof. In some embodiments, the LPA-associated disease is an LPA_1-associated disease, such as, but not limited to, fibrosis, transplant rejection, cancer, osteoporosis, or an inflammatory disorder.

[0008] In some embodiments, the LPA-associated disease is fibrosis, transplant rejection, cancer, osteoporosis, or inflammatory disorders. In certain of these embodiments, the fibrosis is pulmonary, liver, renal, cardiac, dermal, ocular, or pancreatic fibrosis. In certain embodiments, the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder,

genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.

[0009] In some embodiments, the LPA-associated disease is idiopathic pulmonary fibrosis (IPF), non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, diabetic kidney disease, systemic sclerosis, COVID-19, chronic obstructive pulmonary disease (COPD), neuroinflammation, or multiple sclerosis.

[0010] Also provided herein are methods for treating or preventing fibrosis in a subject in need thereof, the method comprising administering to subject a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, or a pharmaceutical composition thereof.

[0011] In some embodiments, the fibrosis is idiopathic pulmonary fibrosis (IPF), nonalcoholic steatohepatitis (NASH), chronic kidney disease, diabetic kidney disease, and systemic sclerosis. For example, the fibrosis can be IPF.

DETAILED DESCRIPTION

Definitions

[0012] The following description sets forth exemplary embodiments of the present technology. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

[0013] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0014] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-C(O)NH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or named.

[0015] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-6} alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0016] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0017] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_{1-20} alkyl), 1 to 12 carbon atoms (i.e., C_{1-12} alkyl), 1 to 8 carbon atoms (i.e., C_{1-8} alkyl), 1 to 6 carbon atoms (i.e., C_{1-6} alkyl), or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., $-(CH_2)_3CH_3$), sec-butyl (i.e., $-CH(CH_3)CH_2CH_3$), isobutyl (i.e., $-CH_2CH(CH_3)_2$), and tert-butyl (i.e., $-C(CH_3)_3$), and "propyl" includes n-propyl (i.e., $-(CH_2)_2CH_3$), and isopropyl (i.e., $-CH(CH_3)_2$).

[0018] "Alkenyl" refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 12 carbon atoms (i.e., C_{2-12} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, e.g., ethenyl, propenyl, butadienyl (including 1,2-butadienyl, and 1,3-butadienyl).

[0019] "Alkynyl" refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 12 carbon atoms (i.e., C_{2-12} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0020] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group or an "arylenyl" group, respectively.

[0021] "Alkoxy" refers to the group "alkyl-O-". Examples of alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0022] "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0023] "Haloalkoxy" refers to an alkoxy group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0024] "Hydroxyalkyl" refers to an alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a hydroxy group.

[0025] "Alkylthio" refers to the group "alkyl-S-".

[0026] "Acyl" refers to a group -C(O)R, wherein R is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include formyl, acetyl, cylcohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0027] "Amido" refers to both a "C-amido" group which refers to the group $-C(O)NR^yR^z$ and an "N-amido" group which refers to the group $-NR^yC(O)R^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of which may be optionally substituted, as defined herein.

[0028] "Amino" refers to the group $-NR^yR^z$ wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0029] "Amidino" refers to $-C(NR^y)(NR^z{}_2)$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0030] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring

carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl regardless of point of attachment. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl regardless of point of attachment. If one or more aryl groups are fused with a cycloalkyl, the resulting ring system is cycloalkyl regardless of point of attachment.

[0031] "Carbamoyl" refers to both an "O-carbamoyl" group which refers to the group $-O-C(O)NR^yR^z$ and an "N-carbamoyl" group which refers to the group $-NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0032] "Carboxyl ester" or "ester" refer to both $-OC(O)R^x$ and $-C(O)OR^x$, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0033] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 14 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes "spirocycloalkyl" when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[0034] "Imino" refers to a group $-C(NR^y)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0035] "Halogen" or "halo" refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0036] "Heteroalkyl" refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. The term "heteroalkyl" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR-, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, where R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or heterocyclyl, each of which may be optionally substituted. Examples of heteroalkyl groups include $-OCH_3$, $-CH_2OCH_3$, $-SCH_3$, $-CH_2SCH_3$, $-NRCH_3$, and $-CH_2NRCH_3$, where R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. As used herein, heteroalkyl include 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0037] "Heteroalkylene" refers to a divalent heteroalkyl group. "Heteroalkylene" groups must have at least one carbon and at least one heteroatomic group within the chain. The term "heteroalkylene" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, $-NR^y-$, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkylene groups include, e.g., $-CH_2OCH_2-$, $-CH(CH_3)OCH_2-$, $-CH_2CH_2OCH_2-$, $-OCH_2-$, $-CH(CH_3)O-$, $-CH_2CH_2O-$, $-CH_2CH_2OCH_2CH_2OCH_2-$, $-CH_2CH_2OCH_2CH_2O-$, $-CH_2SCH_2-$, $-CH(CH_3)SCH_2-$, $-CH_2CH_2SCH_2-$, $-CH_2CH_2SCH_2CH_2SCH_2-$, $-SCH_2-$, $-CH(CH_3)S-$, $-CH_2CH_2S-$, $-CH_2CH_2SCH_2CH_2S-$, $-CH_2S(O)_2CH_2-$, $-CH(CH_3)S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_2-$, $-CH_2NR^yCH_2-$, $-CH(CH_3)NR^yCH_2-$, $-CH_2CH_2NR^yCH_2-$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_2-$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkylene includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom. As used herein, the term "heteroalkylene" does not include groups such as amides or other functional groups having an oxo present on one or more carbon atoms.

[0038] "Heteroaryl" refers to an aromatic group having a single ring or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (i.e., C_{3-12}

heteroaryl), or 3 to 8 carbon ring atoms (i.e., C_{3-8} heteroaryl), and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothienyl (dibenzothiophenyl), furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiophenyl (thienyl), thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thienyl (benzo[b]thiophenyl), indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound *via* either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0039] "Heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro, and may comprise one or more (e.g., 1 to 3) oxo (=O) or N-oxide ($-O^-$) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloalkyl, an aryl, or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C_{2-20} heterocyclyl), 2 to 12 ring carbon atoms (i.e., C_{2-12} heterocyclyl), 2 to 10 ring carbon atoms (i.e., C_{2-10} heterocyclyl), 2 to 8 ring carbon atoms (i.e., C_{2-8} heterocyclyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heterocyclyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4

ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur, or oxygen. Examples of heterocyclyl groups include, e.g., azetidinyl, azepinyl, benzodioxolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl, indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, tetrahydrothiophenyl (benzo[b]thienyl), thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. The term "heterocyclyl" also includes "spiroheterocyclyl" when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as oxabicyclo[2.2.2]octanyl, 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound *via* either ring of the fused system.

[0040] "Sulfonyl" refers to the group $-S(O)_2R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0041] "Alkylsulfonyl" refers to the group $-S(O)_2R$, where R is alkyl.

[0042] "Alkylsulfinyl" refers to the group -S(O)R, where R is alkyl.

[0043] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0044] As used herein, the term "compound," is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

[0045] Some of the compounds exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown, and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0046] Any compound or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. These forms of compounds may also be referred to as "isotopically enriched analogs." Isotopically labeled compounds have structures depicted herein, except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0047] The term "isotopically enriched analogs" includes "deuterated analogs" of compounds described herein in which one or more hydrogens is/are replaced by deuterium, such as a hydrogen on a carbon atom. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0048] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements, and/or an improvement in therapeutic index. An ^{18}F, ^{3}H, ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled

reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[0049] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0050] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0051] Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein. "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0052] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include, e.g., acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts.

Salts derived from organic bases include, but are not limited to, salts of NH_3, or primary, secondary, tertiary amines, such as salts derived from a N-containing heterocycle, a N-containing heteroaryl, or derived from an amine of formula $N(R^N)_3$ (e.g., $HN^+(R^N)_3$ or $(alkyl)N^+(R^N)_3$) where each R^N is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each is optionally substituted, such as by one or more (e.g., 1-5 or 1-3) substituents (e.g., halo, cyano, hydroxy, amino, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, or haloalkoxy). Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0053] The term "substituted" means that any one or more hydrogen atoms on the designated atom or group is replaced with one or more substituents other than hydrogen, provided that the designated atom's normal valence is not exceeded. The one or more substituents include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, alkylsulfinyl, sulfonic acid, alkylsulfonyl, thiocyanate, thiol, thione, or combinations thereof.

[0054] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl) substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term "substituted" may describe other chemical groups defined herein. Unless specified otherwise, where a group is described as optionally substituted, any substituents of the group are themselves unsubstituted. For example, in some embodiments, the term "substituted alkyl" refers to an alkyl group having one or more substituents including hydroxyl, halo, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl. In other embodiments, the one or more substituents may be further substituted with halo, alkyl, haloalkyl, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted. In other embodiments, the substituents may be further substituted with halo, alkyl, haloalkyl, alkoxy, hydroxyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is unsubstituted.

[0055] As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0056] A "solvate" is formed by the interaction of a solvent and a compound. Solvates of salts of the compounds described herein are also provided. Hydrates of the compounds described herein are also provided.

[0057] The term "LPA-associated disease" as used herein is meant to include, without limitation, those diseases, disorders, or conditions in which activation of at least one LPA receptor by LPA contributes to the symptomology or progression of the disease, disorder or condition. These diseases, disorders, or conditions may arise from one or more of a genetic, iatrogenic, immunological, infectious, metabolic, oncological, toxic, surgical, and/or traumatic etiology. Accordingly, inhibiting of one or more lysophosphatidic acid (LPA) receptors (e.g., LPA_1, LPA_2, LPA_3, LPA_4, LPA_5, or LPA_6 receptor) signaling can alter the pathology and/or symptoms and/or progression of the disease, disorder, or condition. In some embodiments, the LPA-associated disease is an LPA1-associated disease, wherein modulating LPA1 receptor signaling can alter the pathology and/or symptoms and/or progression of the disease, disorder, or condition.

[0058] The terms "fibrosis" or "fibrosing disorder," as used herein, refers to conditions that are associated with the abnormal accumulation of cells and/or fibronectin and/or collagen and/or increased fibroblast recruitment and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, liver, joints, lung, pleural tissue, peritoneal tissue, skin, cornea, retina, musculoskeletal and digestive tract.

[0059] The term "pharmaceutically acceptable" as used herein indicates that the compound, or salt or composition thereof is compatible chemically and/or toxicologically with the other ingredients comprising a formulation and/or the subject being treated therewith.

[0060] The term "administration" or "administering" refers to a method of giving a dosage of a compound or pharmaceutical composition to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian. The method of administration can vary depending on various factors, e.g., the components of the pharmaceutical composition, the site of the disease, and the severity of the disease.

[0061] The terms "effective amount" or "effective dosage" or "pharmaceutically effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a chemical entity (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated, and can include curing the disease. "Curing" means that the symptoms of active disease are eliminated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study. In some embodiments, a "therapeutically effective amount" of a compound as provided herein refers to an amount of the compound that is effective as a monotherapy or combination therapy.

[0062] The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In some embodiments, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; Handbook of Pharmaceutical Excipients, 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; Handbook of Pharmaceutical Additives, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; Pharmaceutical Preformulation and Formulation, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

[0063] The term "pharmaceutical composition" refers to a mixture of a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof as provided herein with other chemical components (referred to collectively herein as "excipients"), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

[0064] The terms "treat," "treating," and "treatment," in the context of treating a disease, disorder, or condition, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more

of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof.

[0065] The term "preventing," as used herein, is the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

[0066] The terms "subject," "patient," or "individual," as used herein, are used interchangeably and refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the term refers to a subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired or needed. In some embodiments, the subject is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease, disorder, or condition to be treated and/or prevented.

[0067] The terms "treatment regimen" and "dosing regimen" are used interchangeably to refer to the dose and timing of administration of each therapeutic agent in a combination.

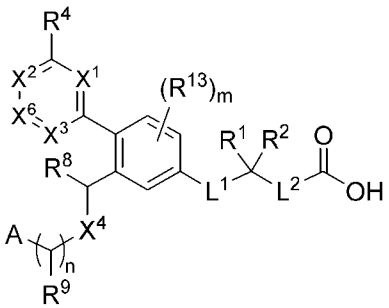
[0068] The term "pharmaceutical combination," as used herein, refers to a pharmaceutical treatment resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients.

[0069] The term "combination therapy" as used herein refers to a dosing regimen of two different therapeutically active agents (i.e., the components or combination partners of the combination), wherein the therapeutically active agents are administered together or separately in a manner prescribed by a medical care taker or according to a regulatory agency as defined herein.

[0070] The term "modulate," "modulating," or "modulation," as used herein, refers to a regulation or an adjustment (e.g., increase or decrease) and can include, for example agonism, partial agonism or antagonism.

Compounds

[0071] In one aspect, provided herein is a compound of Formula I:



I

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of A is independently optionally substituted with one to five Z^1;

L^1 is a bond, -O-, -S-, -S(O)-, $-S(O)_2-$, $-NR^{10}-$, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^1 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

L^2 is a bond, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^2 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

X^1 is N or CR^3;

X^2 is N or CR^5;

X^3 is N or CR^7;

X^4 is O or CHR^{11}; provided that when A is C_{1-6} alkyl, then X^4 is O;

X^6 is N or CR^6;

n is 0, 1, or 2;

m is 0, 1, 2, or 3;

R^1 and R^2 are each independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl of R^1 and R^2 are independently optionally substituted with one to five Z^1;

or R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-10} cycloalkyl or heterocyclyl; wherein the C_{3-10} cycloalkyl or heterocyclyl is optionally substituted by one to five Z^1;

R^3 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, $-N(C_{1-5}$ alkyl$)_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, $-N(C_{1-5}$ alkyl$)_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^3 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^4 is halo, cyano, nitro, -OR^{14}, -$N(R^{14})_2$, -SR^{14}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^4 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, C_{1-5} alkoxy, and cyano;

or R^3 and R^4 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^5 is hydrogen, halo, cyano, nitro, -OR^{15}, -$N(R^{15})_2$, -SR^{15}, -$C(O)R^{15}$, -$C(O)OR^{15}$, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl of R^5 is independently optionally substituted with one to five Z^1;

R^6 is hydrogen, halo, cyano, nitro, -OR^{16}, -$N(R^{16})_2$, -SR^{16}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^6 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^7 is hydrogen, halo, cyano, nitro, -OH, -SH, -NH_2, -NH-C_{1-5} alkyl, -$N(C_{1-5}$ alkyl$)_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -$N(C_{1-5}$ alkyl$)_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^7 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

or R^6 and R^7 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^8 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^9 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^{10} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{10} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{11} is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

each R^{13} is independently hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl of R^{13} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{14} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{14} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{15} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{15} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{16} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{16} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

each Z^1 is independently halo, cyano, nitro, oxo, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-H, -L-C_{1-9} alkyl, -L-C_{2-9} alkenyl, -L-C_{2-9} alkynyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^1 is independently optionally substituted with one to five Z^{1a};

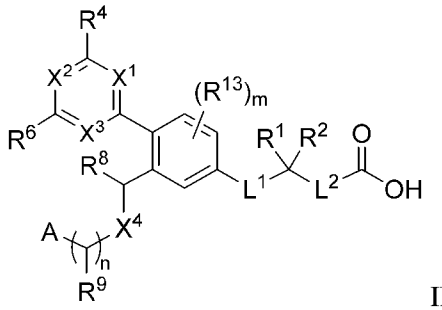
each L is independently -O-, -S-, -NR^{20}-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NR^{20}-, -NR^{20}C(O)-, -OC(O)NR^{20}-, -NR^{20}C(O)O-, -NR^{20}C(O)NR^{21}-, -S(O)-, -$S(O)_2$-, -S(O)NR^{20}-, -$S(O)_2NR^{20}$-, -NR^{20}S(O)-, -$NR^{20}S(O)_2$-, -NR^{20}S(O)NR^{21}-, or -$NR^{20}S(O)_2NR^{21}$-;

each R^{20} and R^{21} is independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{20} and R^{21} is independently optionally substituted with one to five Z^{1a}; or an R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to five Z^{1a}; and

each Z^{1a} is independently halo, hydroxy, cyano, nitro, oxo, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl,

heterocyclyl, aryl, or heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1a} is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

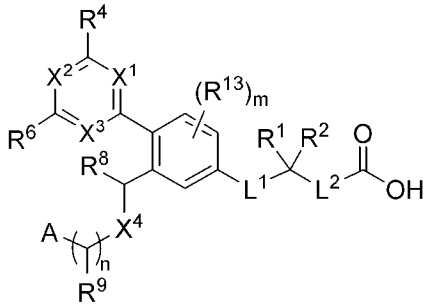
[0072] In some embodiments, provided herein is a compound of Formula II:



II

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of A, R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, n, m, L^1, and L^2 are independently as defined herein.

[0073] In some embodiments, provided herein is a compound of Formula II:



II

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of A is independently optionally substituted with one to five Z^1;

L^1 is a bond, -O-, -S-, -S(O)-, -S(O)$_2$-, -NR^{10}-, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^1 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

L^2 is a bond, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^2 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

X^1 is N or CR^3;

X^2 is N or CR^5;

X^3 is N or CR^7;

X^4 is O or CHR^{11}; provided that when A is C_{1-6} alkyl, then X^4 is O;

n is 0, 1, or 2;

m is 0, 1, 2, or 3;

R^1 and R^2 are each independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl of R^1 and R^2 are independently optionally substituted with one to five Z^1;

or R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-10} cycloalkyl or heterocyclyl; wherein the C_{3-10} cycloalkyl or heterocyclyl is optionally substituted by one to five Z^1;

R^3 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^3 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^4 is halo, cyano, nitro, $-OR^{14}$, $-N(R^{14})_2$, $-SR^{14}$, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^4 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, C_{1-5} alkoxy, and cyano;

or R^3 and R^4 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^5 is hydrogen, halo, cyano, nitro, $-OR^{15}$, $-N(R^{15})_2$, $-SR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl of R^5 is independently optionally substituted with one to five Z^1;

R^6 is hydrogen, halo, cyano, nitro, $-OR^{16}$, $-N(R^{16})_2$, $-SR^{16}$, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^6 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^7 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, $-NH-C_{1-5}$ alkyl, $-N(C_{1-5}$ alkyl$)_2$, $-S-C_{1-5}$ alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the $-NH-C_{1-5}$ alkyl, $-N(C_{1-5}$ alkyl$)_2$, $-S-C_{1-5}$ alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^7 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

or R^6 and R^7 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^8 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^9 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^{10} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{10} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{11} is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

each R^{13} is independently hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, $-NH-C_{1-9}$ alkyl, $-N(C_{1-9}$ alkyl$)_2$, $-S-C_{1-9}$ alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl; wherein each $-NH-C_{1-9}$ alkyl, $-N(C_{1-9}$ alkyl$)_2$, $-S-C_{1-9}$ alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl of R^{13} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{14} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{14} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{15} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered

heterocyclyl of R^{15} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{16} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{16} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

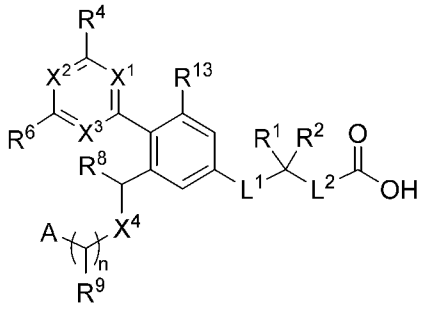
each Z^1 is independently halo, cyano, nitro, oxo, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-H, -L-C_{1-9} alkyl, -L-C_{2-9} alkenyl, -L-C_{2-9} alkynyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^1 is independently optionally substituted with one to five Z^{1a};

each L is independently -O-, -S-, -NR^{20}-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NR^{20}-, -NR^{20}C(O)-, -OC(O)NR^{20}-, -NR^{20}C(O)O-, -NR^{20}C(O)NR^{21}-, -S(O)-, -$S(O)_2$-, -S(O)NR^{20}-, -$S(O)_2NR^{20}$-, -NR^{20}S(O)-, -$NR^{20}S(O)_2$-, -NR^{20}S(O)NR^{21}-, or -$NR^{20}S(O)_2NR^{21}$-;

each R^{20} and R^{21} is independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{20} and R^{21} is independently optionally substituted with one to five Z^{1a}; or an R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to five Z^{1a}; and

each Z^{1a} is independently halo, hydroxy, cyano, nitro, oxo, -SH, -NH_2, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1a} is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

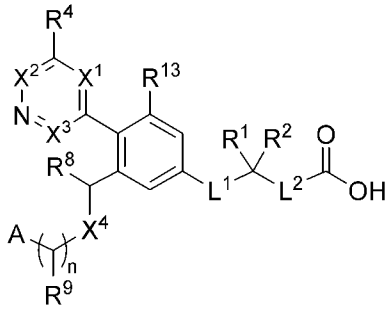
[0074] In some embodiments, provided herein is a compound of Formula IXA:



IXA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of A, R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, n, L^1, and L^2 are independently as defined herein.

[0075] In some embodiments, provided herein is a compound of Formula IXB:

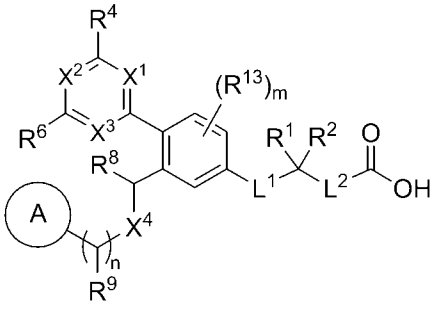


IXB

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of A, R^1, R^2, R^4, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, n, L^1, and L^2 are independently as defined herein.

[0076] In some embodiments, A is C_{1-6} alkyl. In some embodiments, A is C_{3-4} alkyl. In some embodiments, A is n-propyl, n-butyl, isopropyl, or isobutyl.

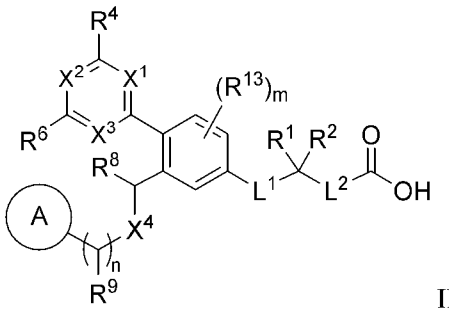
[0077] In one aspect, provided herein is a compound of Formula IIA:



IIA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, n, m, L^1, and L^2 are independently as defined herein, and ring A is C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of ring A is independently optionally substituted with one to five Z^1.

[0078] In one aspect, provided herein is a compound of Formula IIA:



IIA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

ring A is C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of ring A is independently optionally substituted with one to five Z^1;

L^1 is a bond, -O-, -S-, -S(O)-, -S(O)$_2$-, -NR^{10}-, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^1 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

L^2 is a bond, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^2 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

X^1 is N or CR^3;

X^2 is N or CR^5;

X^3 is N or CR^7;

X^4 is O or CHR^{11};

n is 0, 1, or 2;

m is 0, 1, 2, or 3;

R^1 and R^2 are each independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl of R^1 and R^2 are independently optionally substituted with one to five Z^1;

or R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-10} cycloalkyl or heterocyclyl; wherein the C_{3-10} cycloalkyl or heterocyclyl is optionally substituted by one to five Z^1;

R^3 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^3 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^4 is halo, cyano, nitro, -OR^{14}, -N(R^{14})$_2$, -SR^{14}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^4 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

or R^3 and R^4 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^5 is hydrogen, halo, cyano, nitro, -OR^{15}, -N(R^{15})$_2$, -SR^{15}, -C(O)R^{15}, -C(O)OR^{15}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl of R^5 is independently optionally substituted with one to five Z^1;

R^6 is hydrogen, halo, cyano, nitro, -OR^{16}, -N(R^{16})$_2$, -SR^{16}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^6 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^7 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^7 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

or R^6 and R^7 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^8 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^9 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^{10} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{10} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{11} is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

each R^{13} is independently hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl of R^{13} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{14} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{14} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{15} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{15} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{16} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{16} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

each Z^1 is independently halo, cyano, nitro, oxo, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-H, -L-C_{1-9} alkyl, -L-C_{2-9} alkenyl, -L-C_{2-9} alkynyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl,

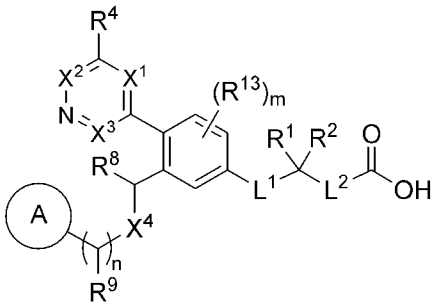
C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^1 is independently optionally substituted with one to five Z^{1a};

each L is independently -O-, -S-, -NR^{20}-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NR^{20}-, -NR^{20}C(O)-, -OC(O)NR^{20}-, -NR^{20}C(O)O-, -NR^{20}C(O)NR^{21}-, -S(O)-, -$S(O)_2$-, -S(O)NR^{20}-, -$S(O)_2NR^{20}$-, -NR^{20}S(O)-, -$NR^{20}S(O)_2$-, -NR^{20}S(O)NR^{21}-, or -$NR^{20}S(O)_2NR^{21}$-;

each R^{20} and R^{21} is independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{20} and R^{21} is independently optionally substituted with one to five Z^{1a}; or an R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to five Z^{1a}; and

each Z^{1a} is independently halo, hydroxy, cyano, nitro, oxo, -SH, -NH_2, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1a} is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

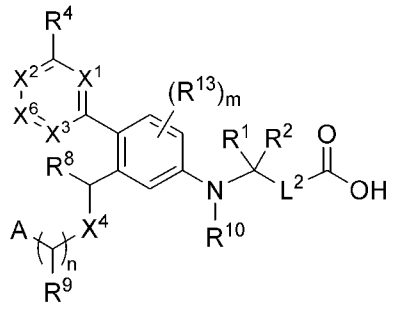
[0079] In one aspect, provided herein is a compound of Formula IIB:



IIB

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, n, m, L^1, and L^2 are independently as defined herein, and ring A is C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of ring A is independently optionally substituted with one to five Z^1.

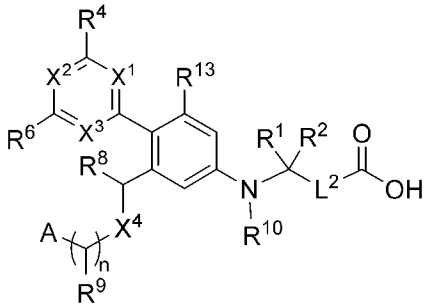
[0080] In one aspect, provided herein is a compound of Formula IIC:



IIC

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^8, R^9, R^{10}, R^{13}, X^1, X^2, X^3, X^4, X^6, A, n, m, and L^2 are independently as defined herein.

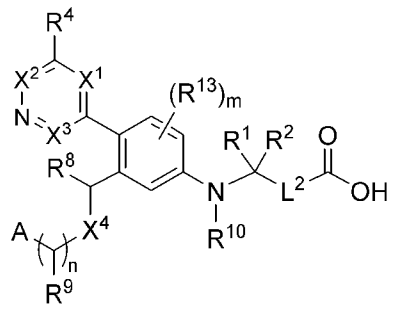
[0081] In one aspect, provided herein is a compound of Formula IID:



IID

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^6, R^8, R^9, R^{10}, R^{13}, X^1, X^2, X^3, X^4, A, n, and L^2 are independently as defined herein.

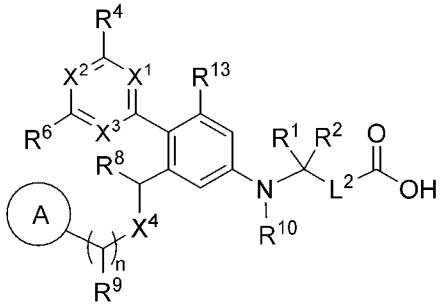
[0082] In one aspect, provided herein is a compound of Formula IIE:



IIE

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^8, R^9, R^{10}, R^{13}, X^1, X^2, X^3, X^4, A, n, m, and L^2 are independently as defined herein.

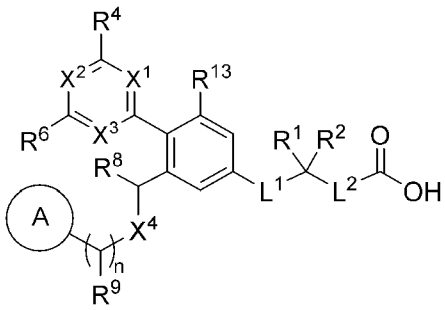
[0083] In one aspect, provided herein is a compound of Formula IIF:



IIF

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^6, R^8, R^9, R^{10}, R^{13}, X^1, X^2, X^3, X^4, ring A, n, and L^2 are independently as defined herein.

[0084] In some embodiments, the compound of Formula I or II is represented by Formula IA:



IA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, ring A, n, L^1, and L^2 are independently as defined herein.

[0085] In some embodiments, X^1 is N. In some embodiments, X^1 is CR^3.

[0086] In some embodiments, X^2 is N. In some embodiments, X^2 is CR^5.

[0087] In some embodiments, X^3 is N. In some embodiments, X^3 is CR^7.

[0088] In some embodiments, X^1 is N, X^2 is N, and X^3 is N. In some embodiments, X^1 is N, X^2 is N, and X^3 is CR^7. In some embodiments, X^1 is N, X^2 is CR^5, and X^3 is N. In some embodiments, X^1 is CR^3, X^2 is N, and X^3 is N. In some embodiments, X^1 is CR^3, X^2 is N, and X^3 is CR^7. In some embodiments, X^1 is CR^3, X^2 is CR^5, and X^3 is N. In some embodiments, X^1 is CR^3, X^2 is CR^5, and X^3 is CR^7. In some embodiments, X^1 is N, X^2 is CR^5, and X^3 is CR^7.

[0089] In some embodiments, R^3 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^3 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano.

[0090] In some embodiments, R^3 is hydrogen, halo, or C_{1-5} alkyl, wherein the C_{1-5} alkyl is optionally substituted with one to five halo. In some embodiments, R^3 is hydrogen, halo, C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^3 is hydrogen, fluoro, chloro, methyl, ethyl, or difluoromethyl. In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is halo. In some embodiments, R^3 is C_{1-5} alkyl. In some embodiments, R^3 is C_{1-5} haloalkyl.

[0091] In some embodiments, R^4 is -OR^{14}, -N(R^{14})$_2$, or C_{1-5} alkyl, wherein the C_{1-5} alkyl is optionally substituted with hydroxy or C_{1-5} alkoxy. In some embodiments, R^4 is -OR^{14} or C_{1-5} alkyl, wherein the C_{1-5} alkyl is optionally substituted with hydroxy or C_{1-5} alkoxy.

[0092] In some embodiments, R^4 is -OR^{14} or -N(R^{14})$_2$. In some embodiments, R^4 is -O-C_{1-5} alkyl, -O-C_{3-5} cycloalkyl, or -NH-C_{1-5} alkyl. In some embodiments, R^4 is methoxy, ethoxy, iso-butoxy, cyclopropoxy, or ethylamino.

[0093] In some embodiments, R^4 is -OR^{14}. In some embodiments, R^4 is -O-C_{1-5} alkyl. In some embodiments, R^4 is hydroxy, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, cyclopropoxy, cyclobutoxy, methyl, ethyl, *n*-propyl, *iso*-propyl, 2-hydroxyethyl, or methoxymethyl. In some embodiments, R^4 is -OR^{14}, and R^{14} is C_{1-5} alkyl or C_{3-5} cycloalkyl. In some embodiments, R^4 is hydroxy, methoxy, ethoxy, *n*-propoxy, cyclopropoxy, cyclobutoxy, methyl, ethyl, *n*-propyl, 2-hydroxyethyl, or methoxymethyl. In some embodiments, R^4 is hydroxy, methoxy, ethoxy, or cyclopropyloxy. In some embodiments, R^4 is hydroxy, methoxy, or ethoxy. In some embodiments, R^4 is methoxy or ethoxy. In some embodiments, R^4 is methoxy. In some embodiments, R^4 is ethoxy. In some embodiments, R^4 is cyclopropyloxy.

[0094] In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano.

[0095] In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a cycloalkyl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a C_6 cycloalkyl optionally substituted with one to five substituents independently

selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a C_5 cycloalkyl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, the cycloalkyl is unsubstituted.

[0096] In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form an aryl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a C_6 aryl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, the aryl is unsubstituted.

[0097] In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a heterocyclyl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a 5 or 6 membered heterocyclyl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a 5 membered heterocyclyl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a 5 membered oxygen containing heterocyclyl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, the heterocyclyl is unsubstituted.

[0098] In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a heteroaryl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a 5 or 6 membered heteroaryl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, R^3 and R^4 are taken together with the atoms to which they are attached to form a 6 membered heteroaryl optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano. In some embodiments, the heteroaryl is unsubstituted.

[0099] In some embodiments, R^6 is hydrogen, cyano, $-OR^{16}$, or C_{1-5} alkyl. In some embodiments, R^6 is hydrogen, cyano, $-O-C_{1-5}$ alkyl, or C_{1-5} alkyl. In some embodiments, R^6 is $-OR^{16}$. In some embodiments, R^6 is $-O-C_{1-5}$ alkyl. In some embodiments, R^6 is hydroxy, cyano, methoxy, or ethoxy. In some embodiments, R^6 is methoxy.

[0100] In some embodiments, R^4 is $-OR^{14}$ or $-N(R^{14})_2$ and R^6 is hydrogen, cyano, $-OR^{16}$, or C_{1-5} alkyl. In some embodiments, R^4 is -O-C_{1-5} alkyl, -O- C_{3-5} cycloalkyl, or -NH-C_{1-5} alkyl and R^6 is hydrogen, cyano, -O-C_{1-5} alkyl, or C_{1-5} alkyl. In some embodiments, R^4 is methoxy, ethoxy, iso-butyloxy, cyclopropoxy, or ethylamino and R^6 is hydroxy, cyano, methoxy, or ethoxy.

[0101] In some embodiments, R^4 is -O-C_{1-5} alkyl and R^6 is hydrogen, cyano, $-OR^{16}$, or C_{1-5} alkyl. In some embodiments, R^4 is -O-C_{1-5} alkyl and R^6 is hydrogen, cyano, -O-C_{1-5} alkyl, or C_{1-5} alkyl. In some embodiments, R^4 is -O-C_{1-5} alkyl and R^6 is $-OR^{16}$. In some embodiments, R^4 is -O-C_{1-5} alkyl and R^6 is -O-C_{1-5} alkyl. In some embodiments, R^4 is -O-C_{1-5} alkyl and R^6 is hydroxy, cyano, methoxy, or ethoxy. In some embodiments, R^4 is -O-C_{1-5} alkyl and R^6 is methoxy. In some embodiments, R^4 is methoxy and R^6 is hydrogen. In some embodiments, R^4 is methoxy and R^6 is methoxy.

[0102] In some embodiments, R^5 is hydrogen, halo, cyano, -C(O)-C_{1-5} alkyl, or C_{1-5} alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, and C_{1-5} alkoxy. In some embodiments, R^5 is hydrogen, cyano, -C(O)-C_{1-5} alkyl, or C_{1-5} alkyl optionally substituted with one to three substituents independently selected from halo and hydroxy. In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is cyano. In some embodiments, R^5 is halo. In some embodiments, R^5 is fluoro. In some embodiments, R^5 is -C(O)-C_{1-5} alkyl. In some embodiments, R^5 is C_{1-5} alkyl optionally substituted with one to three substituents independently selected from halo and hydroxy. In some embodiments, R^5 is C_{1-5} haloalkyl.

[0103] In some embodiments, R^4 is -O-C_{1-5} alkyl, R^5 is hydrogen, cyano, -C(O)-C_{1-5} alkyl, or C_{1-5} alkyl optionally substituted with one to three substituents independently selected from halo and hydroxy, and R^6 is hydrogen, cyano, $-OR^{16}$, or C_{1-5} alkyl.

[0104] In some embodiments, R^7 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^7 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano.

[0105] In some embodiments, R^7 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^7 is hydrogen, fluoro, chloro, methyl, ethyl, or difluoromethyl. In some embodiments, R^7 is hydrogen or C_{1-5} alkyl. In some embodiments, R^7 is hydrogen, methyl, or ethyl. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is halo. In some embodiments, R^7 is C_{1-5} alkyl. In some embodiments, R^7 is C_{1-5} haloalkyl.

[0106] In some embodiments, R^3 is hydrogen and R^7 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^3 is halo and R^7 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^3 is C_{1-5} alkyl and R^7 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^3 is C_{1-5} haloalkyl and R^7 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl.

[0107] In some embodiments, R^3 is hydrogen and R^7 is hydrogen.

[0108] In some embodiments, R^7 is hydrogen and R^3 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^7 is halo and R^3 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^7 is C_{1-5} alkyl and R^3 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R^7 is C_{1-5} haloalkyl and R^3 is hydrogen, halo, or C_{1-5} alkyl, or C_{1-5} haloalkyl.

[0109] In some embodiments, A or ring A is C_{3-10} cycloalkyl or heterocyclyl, wherein each is independently optionally substituted with one to five Z^1. In some embodiments, A or ring A is C_{3-10} cycloalkyl or heterocyclyl.

[0110] In some embodiments, A or ring A is C_{3-10} cycloalkyl optionally substituted with one to five Z^1. In some embodiments, A or ring A is C_{3-10} cycloalkyl optionally substituted with one to five substituents independently selected from halo, hydroxy, cyano, nitro, oxo, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -NHC(O)-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano. In some embodiments, A or ring A is C_{3-10} cycloalkyl optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

[0111] In some embodiments, A or ring A is heterocyclyl optionally substituted with one to five Z^1. In some embodiments, A or ring A is heterocyclyl optionally substituted with one to five substituents independently selected from halo, hydroxy, cyano, nitro, oxo, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -NHC(O)-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano. In some embodiments, A or ring A is heterocyclyl optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

[0112] In some embodiments, A or ring A is aryl optionally substituted with one to five Z^1. In some embodiments, A or ring A is aryl optionally substituted with one to five substituents independently selected from halo, hydroxy, cyano, nitro, oxo, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -NHC(O)-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano. In some embodiments, A or ring A is aryl optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

[0113] In some embodiments, A or ring A is heteroaryl optionally substituted with one to five Z^1. In some embodiments, A or ring A is heteroaryl optionally substituted with one to five substituents independently selected from halo, hydroxy, cyano, nitro, oxo, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -NHC(O)-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano. In some embodiments, A or ring A is heteroaryl optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

[0114] In any embodiment described herein, for groups having two or more substituents, those substituents can be the same or different. For example, in -N(C_{1-5} alkyl)$_2$ or -N(C_{1-9} alkyl)$_2$, the alkyl groups can be the same or different, and where further substituted, those substituents can also be the same or different (e.g., $-N(CH_3)_2$, $-N(CH_3)CH_2CH_3$, $-N(CH_3)CH_2CF_3$, $-N(CHF_2)CH_2CH_2CN$, and the like).

[0115] In some embodiments, X^4 is O. In some embodiments, X^4 is CHR^{11}. In some embodiments, X^4 is CH_2.

[0116] In some embodiments, R^8 is hydrogen.

[0117] In some embodiments, R^9 is hydrogen.

[0118] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 0 or 1. In some embodiments, n is 1 or 2.

[0119] In some embodiments, R^{13} is hydrogen, halo, C_{1-9} alkyl, C_{1-9} haloalkyl, or C_{1-9} alkyl-CN.

[0120] In some embodiments, R^{13} is hydrogen, halo, or C_{1-9} alkyl. In some embodiments, R^{13} is hydrogen.

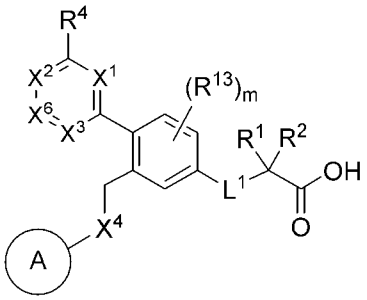
[0121] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 1, and R^{13} is hydrogen, halo, or C_{1-9} alkyl.

[0122] In some embodiments, L^1 is a bond, -O-, -NR^{10}-, C_{1-3} alkylene, or C_{1-3} heteroalkylene. In some embodiments, L^1 is -O-, -NR^{10}-, or C_{1-3} alkylene, and R^{10} is hydrogen or C_{1-9} alkyl. In some embodiments, L^1 is a bond, -O-, -NH-, -NCH_3-, C_{1-3} alkylene, or C_{1-3} heteroalkylene. In some embodiments, L^1 is a bond. In some embodiments, L^1 is -O-. In some embodiments, L^1 is -NR^{10}-. In some embodiments, L^1 is -O- or -NR^{10}-. In some embodiments, L^1 is -NH- or -NCH_3-. In some embodiments, L^1 is -NH-. In some embodiments, L^1 is -O- or -NH-. In some embodiments, L^1 is C_{1-3} alkylene. In some embodiments, L^1 is C_{1-3} heteroalkylene. In some embodiments, L^1 is -O-CH_2-.

[0123] In some embodiments, L^2 is a bond.

[0124] In some embodiments, L^1 is a bond, -O-, -NR^{10}-, C_{1-3} alkylene, or C_{1-3} heteroalkylene, and L^2 is a bond. In some embodiments, L^1 is a bond, -O-, or -NR^{10}-, and L^2 is a bond. In some embodiments, L^1 is -O- or -NR^{10}-, and L^2 is a bond.

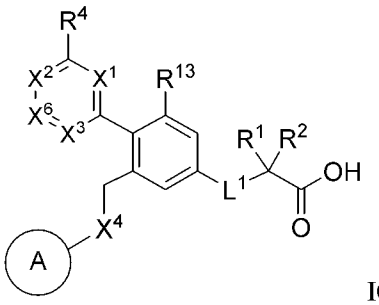
[0125] In some embodiments, provided is a compound of Formula IB:



IB

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^1, R^2, R^4, R^{13}, X^1, X^2, X^3, X^4, X^6, ring A, and L^1 are independently as defined herein.

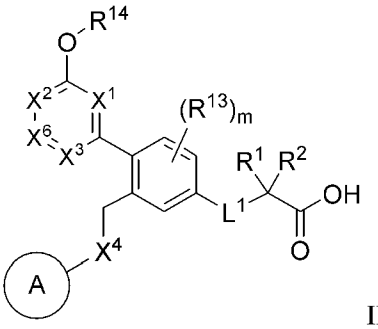
[0126] In some embodiments, provided is a compound of Formula IC:



IC

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^{13}, X^1, X^2, X^3, X^4, X^6, ring A, and L^1 are independently as defined herein.

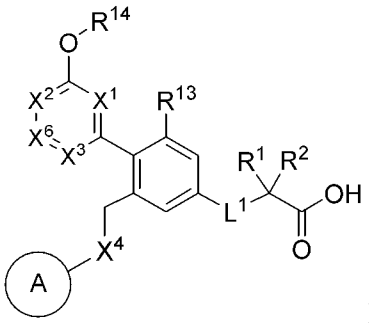
[0127] In some embodiments, provided is a compound of Formula ID:



ID

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^1, R^2, R^6, R^{13}, R^{14}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

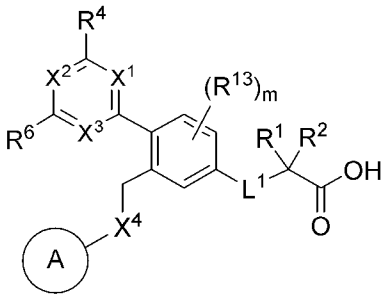
[0128] In some embodiments, provided is a compound of Formula IE:



IE

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^6, R^{13}, R^{14}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

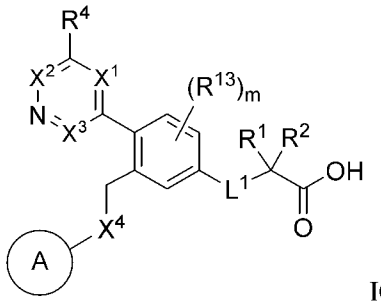
[0129] In some embodiments, provided is a compound of Formula IF:



IF

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^1, R^2, R^4, R^6, R^{13}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

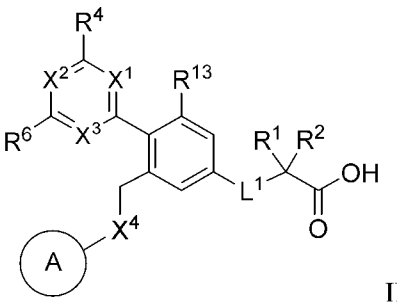
[0130] In some embodiments, provided is a compound of Formula IG:



IG

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^1, R^2, R^4, R^6, R^{13}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

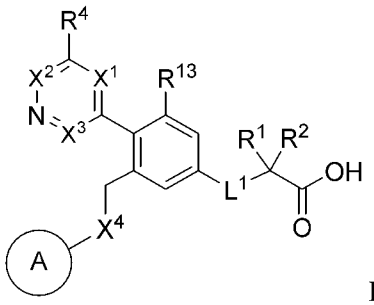
[0131] In some embodiments, provided is a compound of Formula IH:



IH

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^6, R^{13}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

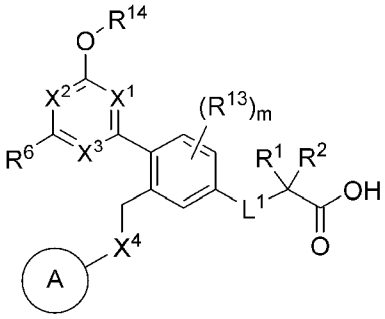
[0132] In some embodiments, provided is a compound of Formula IJ:



IJ

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^4, R^6, R^{13}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

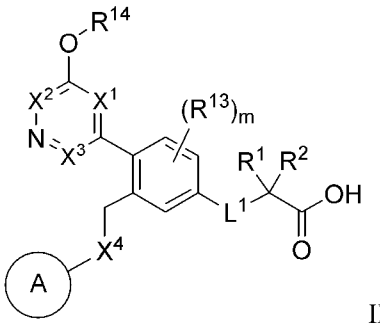
[0133] In some embodiments, provided is a compound of Formula IK:



IK

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^1, R^2, R^6, R^{13}, R^{14}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

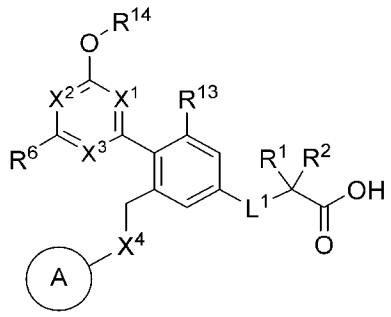
[0134] In some embodiments, provided is a compound of Formula IL:



IL

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^1, R^2, R^6, R^{13}, R^{14}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

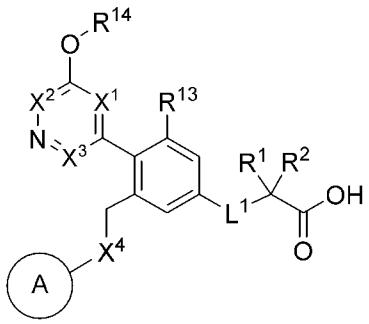
[0135] In some embodiments, provided is a compound of Formula IM:



IM

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^6, R^{13}, R^{14}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

[0136] In some embodiments, provided is a compound of Formula IN:



IN

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^1, R^2, R^6, R^{13}, R^{14}, X^1, X^2, X^3, X^4, ring A, and L^1 are independently as defined herein.

[0137] In some embodiments, R^{14} is C_{1-5} alkyl or C_{3-5} cycloalkyl. In some embodiments, R^{14} is methyl, ethyl, or cyclopropyl.

[0138] In some embodiments, R^{14} is C_{3-5} cycloalkyl. In some embodiments, R^{14} is cyclopropyl. In some embodiments, R^{14} is cyclobutyl.

[0139] In some embodiments, R^{14} is C_{1-5} alkyl. In some embodiments, R^{14} is methyl or ethyl. In some embodiments, R^{14} is methyl. In some embodiments, R^{14} is ethyl.

[0140] In some embodiments, R^1 and R^2 are each independently C_{1-9} alkyl. In some embodiments, R^1 and R^2 are each methyl. In some embodiments, R^1 and R^2 are each hydrogen.

[0141] In some embodiments, R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-10} cycloalkyl optionally substituted by one to five Z^1. In some embodiments, R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-6} cycloalkyl optionally substituted by one to five Z^1. In some embodiments, R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-4} cycloalkyl optionally substituted by one to five Z^1. In some embodiments, the cycloalkyl is unsubstituted. In some embodiments, the cycloalkyl is substituted by one to five halo, hydroxy, C_{1-9} alkyl, C_{1-9} alkoxy, $-CH_2-O-C_{1-9}$ alkyl, or $-NHC(O)O-C_{1-9}$ alkyl.

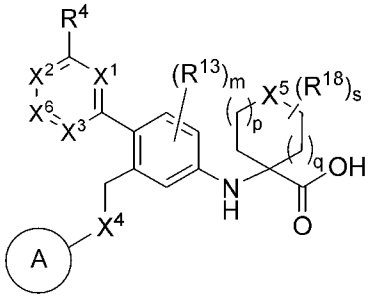
[0142] In some embodiments, R^1 and R^2 are taken together with the atom to which they are attached to form a heterocyclyl optionally substituted by one to five Z^1. In some embodiments, R^1 and R^2 are taken together with the atom to which they are attached to form a 4 to 6 membered heterocyclyl optionally substituted by one to five Z^1. In some embodiments, the heterocyclyl is unsubstituted. In some embodiments, the heterocyclyl is substituted by one to five C_{1-9} alkyl, $-C(O)-C_{1-9}$ alkyl, $-C(O)O-C_{1-9}$ alkyl, or $-C(O)-CH_2-O-C_{1-9}$ alkyl.

[0143] In some embodiments, R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-6} cycloalkyl or a 4 to 6 membered heterocyclyl, wherein each is optionally substituted by one to five halo, hydroxy, C_{1-9} alkyl, C_{1-9} alkoxy, $-CH_2-O-C_{1-9}$ alkyl, $-NHC(O)O-C_{1-9}$ alkyl, $-C(O)-C_{1-9}$ alkyl, $-C(O)O-C_{1-9}$ alkyl, or $-C(O)-CH_2-O-C_{1-9}$ alkyl.

[0144] In some embodiments, R^{13} is hydrogen, halo, or C_{1-9} alkyl.

[0145] In some embodiments, m is 0. In some embodiments, m is 1.

[0146] In some embodiments, provided is a compound of Formula III:



III

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^4, X^6, R^{13}, X^1, X^2, X^3, X^4, and ring A are independently as defined herein.

[0147] In some embodiments, provided is a compound of Formula III, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^4, X^6, R^{13}, X^1, X^2, X^3, X^4, and ring A are independently as defined herein,

p is 0, 1, or 2;

q is 0, 1, or 2;

s is 0, 1, 2, or 3;

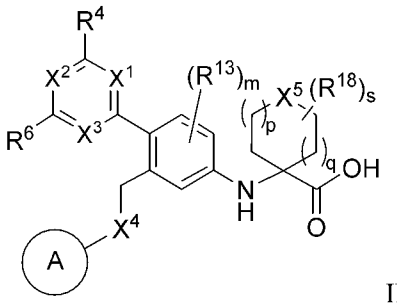
X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

[0148] In some embodiments, m is 1, X^4 is -O-, and R^4 is $-OR^{14}$. In some embodiments, m is 0, X^4 is -O-, and R^4 is $-OR^{14}$. In some embodiments, p is 1, q is 1, m is 0 or 1, X^4 is -O-, and R^4 is $-OR^{14}$.

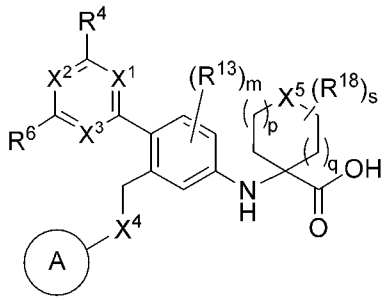
[0149] In some embodiments, provided is a compound of Formula IIIA:



IIIA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^4, R^6, R^{13}, R^{17}, R^{18}, X^1, X^2, X^3, X^4, X^5, p, q, s, and ring A are independently as defined herein.

[0150] In some embodiments, provided is a compound of Formula IIIA:



IIIA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^4, R^6, R^{13}, X^1, X^2, X^3, X^4, and ring A are independently as defined herein:

p is 0, 1, or 2;

q is 0, 1, or 2;

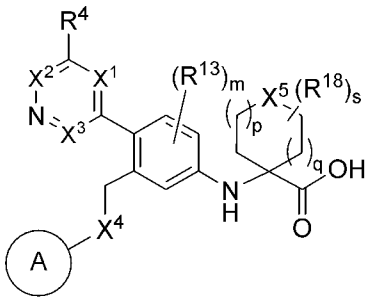
s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

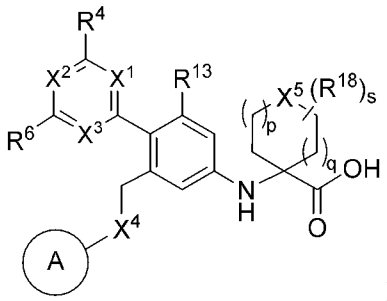
[0151] In some embodiments, provided is a compound of Formula IIIB:



IIIB

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^4, R^{13}, R^{17}, R^{18}, X^1, X^2, X^3, X^4, X^5, p, q, s, and ring A are independently as defined herein.

[0152] In some embodiments, provided is a compound of Formula IIIC:



IIIC

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^4, R^6, R^{13}, X^1, X^2, X^3, X^4, and ring A are independently as defined herein:

p is 0, 1, or 2;

q is 0, 1, or 2;

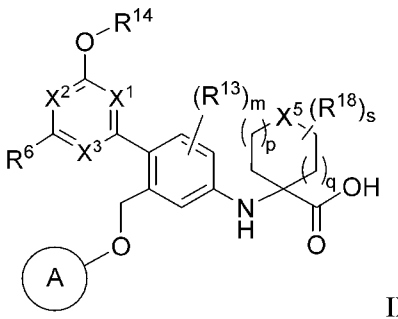
s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

[0153] In some embodiments, provided is a compound of Formula IIID:



IIID

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of m, R^6, R^{13}, R^{14}, X^1, X^2, X^3, and ring A are independently as defined herein:

p is 0, 1, or 2;

q is 0, 1, or 2;

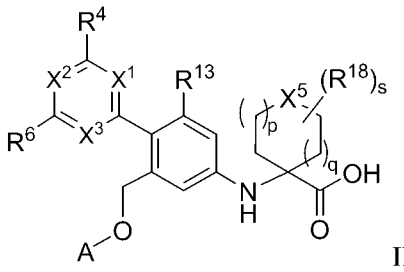
s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

[0154] In some embodiments, provided is a compound of Formula IIIE:



IIIE

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^6, R^{13}, R^{14}, X^1, X^2, X^3, and A are independently as defined herein:

p is 0, 1, or 2;

q is 0, 1, or 2;

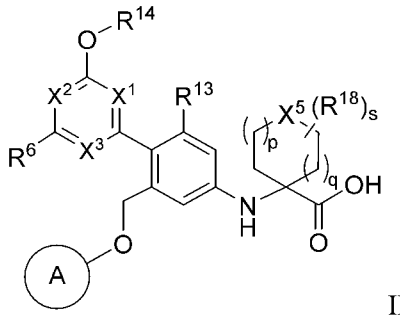
s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

[0155] In some embodiments, provided is a compound of Formula IIIF:



IIIF

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^6, R^{13}, R^{14}, X^1, X^2, X^3, and ring A are independently as defined herein:

p is 0, 1, or 2;

q is 0, 1, or 2;

s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

[0156] In some embodiments, R^{14} is C_{1-5} alkyl. In some embodiments, R^{14} is methyl or ethyl. In some embodiments, R^{14} is methyl. In some embodiments, R^{14} is ethyl.

[0157] In some embodiments, X^5 is absent. In some embodiments, X^5 is O. In some embodiments, X^5 is NR^{17}. In some embodiments, X^5 is $C(R^{18})_2$.

[0158] In some embodiments, each R^{18} is independently hydrogen or Z^1. In some embodiments, each R^{18} is hydrogen. In some embodiments, X^5 is CH_2. In some embodiments, each R^{18} is independently Z^1. In some embodiments, each R^{18} is independently halo. In some embodiments, each R^{18} is fluoro.

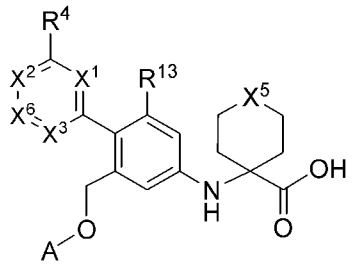
[0159] In some embodiments, R^{17} is hydrogen, C_{1-9} alkyl, $-C(O)R^{20}$, or $-C(O)OR^{20}$.

[0160] In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[0161] In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2.

[0162] In some embodiments, s is 0. In some embodiments, s is 1. In some embodiments, s is 2. In some embodiments, s is 3.

[0163] In some embodiments, provided is a compound of Formula IIIG:

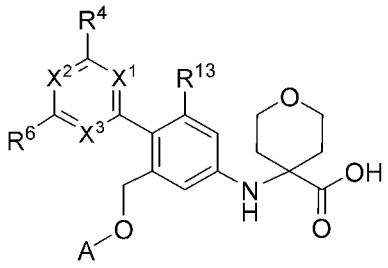


IIIG

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^4, R^{13}, X^1, X^2, X^3, X^5, X^6, and A are independently as defined herein.

[0164] In some embodiments, X^6 is CR^6, In some embodiments, X^6 is N, In some embodiments, X^5 is O. In some embodiments, A is Ring A.

[0165] In some embodiments, provided is a compound of Formula IIIH:

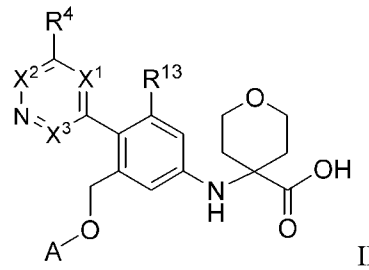


IIIH

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^4, R^6, R^{13}, X^1, X^2, X^3, and A are independently as defined herein.

[0166] In some embodiments, R^{13} is hydrogen. In some embodiments, A is C_{1-6} alkyl. In some embodiments, A is C_{3-4} alkyl. In some embodiments, A is C_{3-10} cycloalkyl or heterocyclyl. In some embodiments, R^4 is -O-R^{14}.

[0167] In some embodiments, provided is a compound of Formula IIIJ:

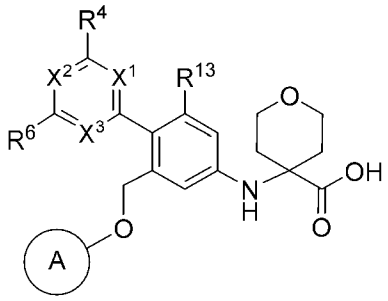


IIIJ

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^4, R^{13}, X^1, X^2, X^3, and A are independently as defined herein.

[0168] In some embodiments, R^{13} is hydrogen. In some embodiments, A is C_{1-6} alkyl. In some embodiments, A is C_{3-4} alkyl. In some embodiments, A is C_{3-10} cycloalkyl or heterocyclyl. In some embodiments, R^4 is -O-R^{14}.

[0169] In some embodiments, provided is a compound of Formula IIIK:



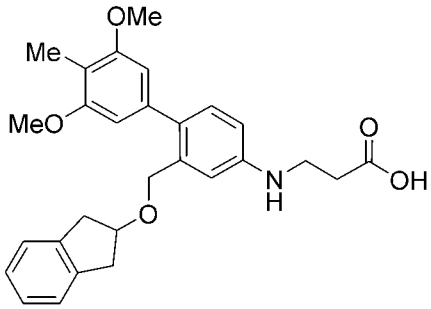
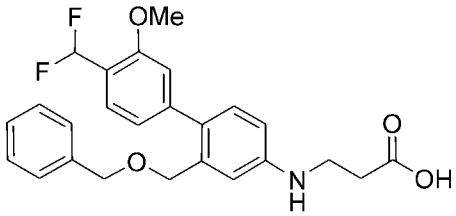
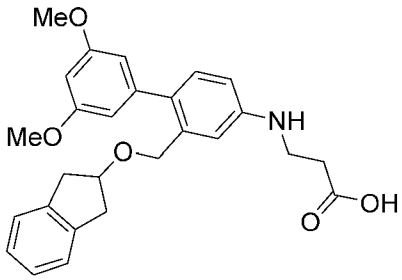
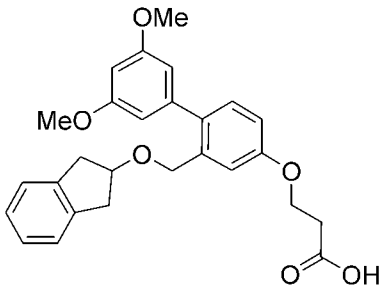
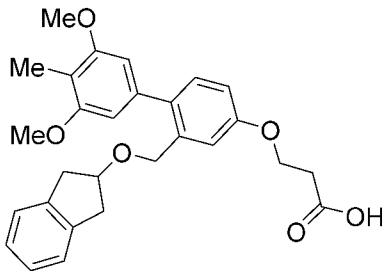
IIIK

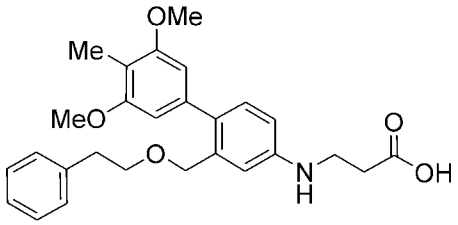
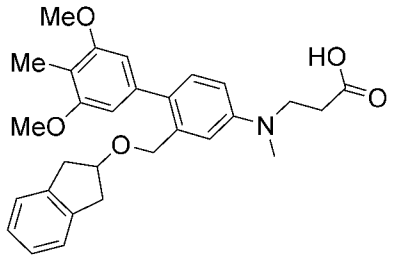
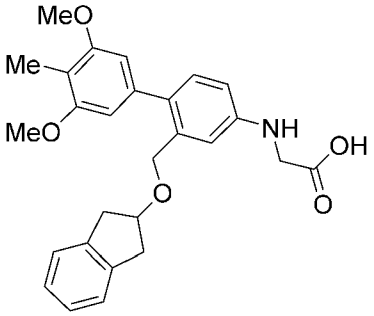
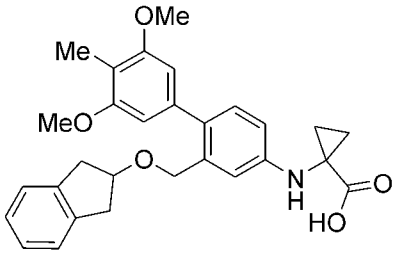
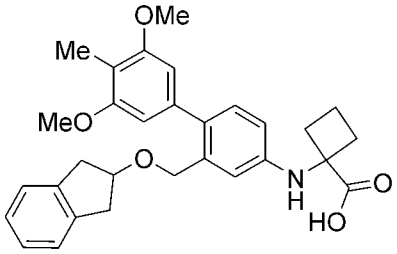
or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein each of R^4, R^6, R^{13}, X^1, X^2, X^3, and ring A are independently as defined herein.

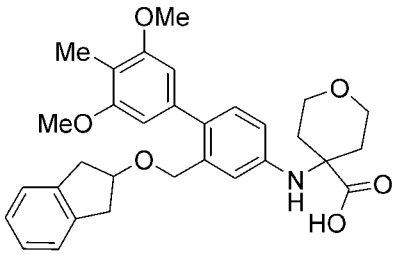
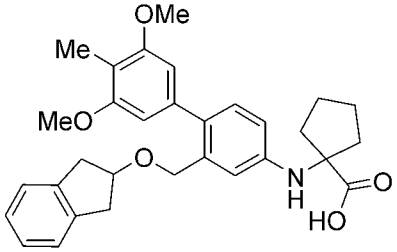
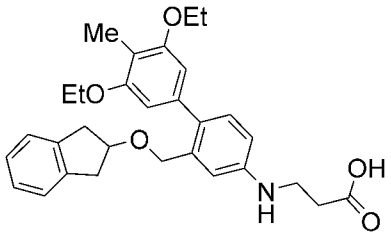
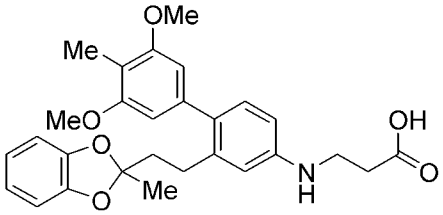
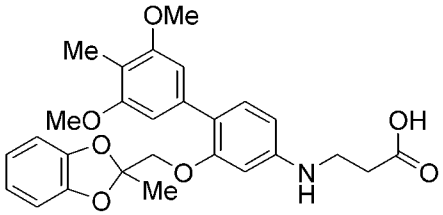
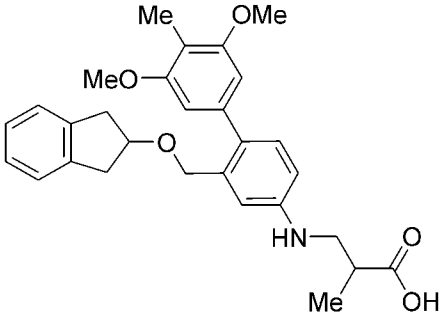
[0170] In some embodiments, R^{13} is hydrogen. In some embodiments, ring A is C_{3-10} cycloalkyl or heterocyclyl. In some embodiments, R^4 is -O-R^{14}.

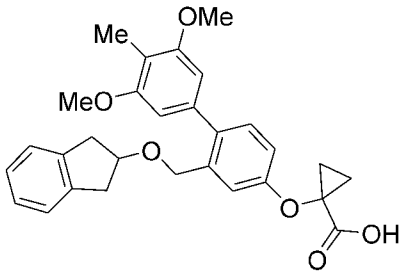
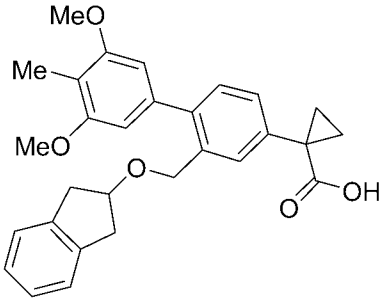
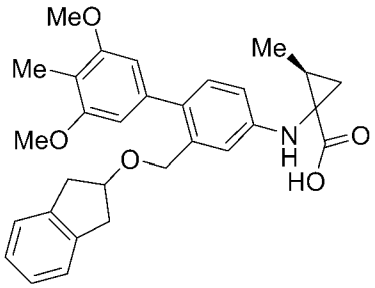
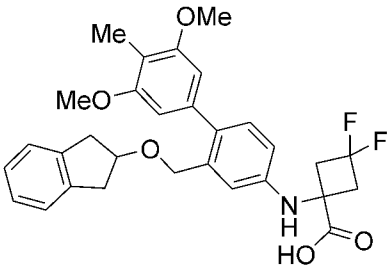
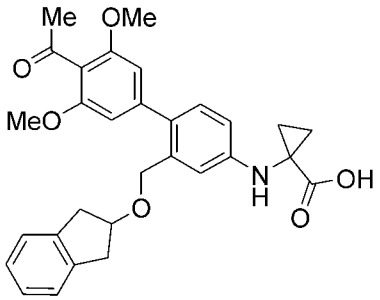
[0171] In some embodiments, provided is compound selected from Table 1, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof:

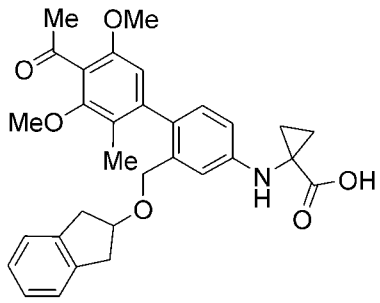
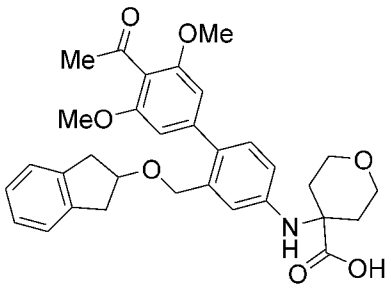
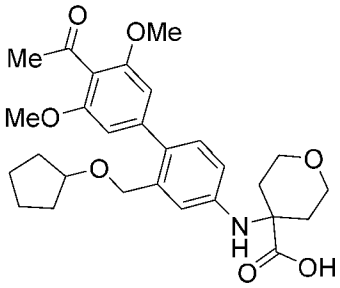
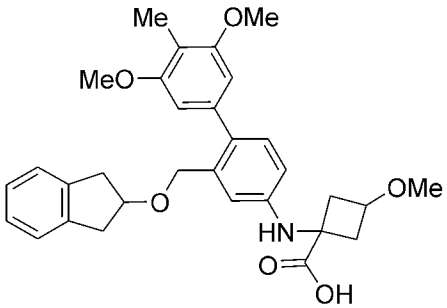
Table 1

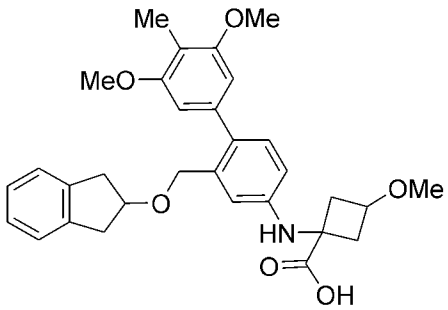
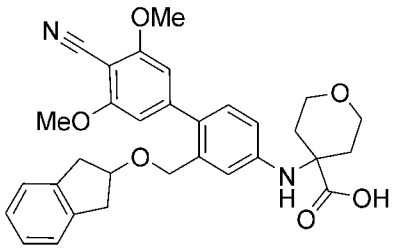
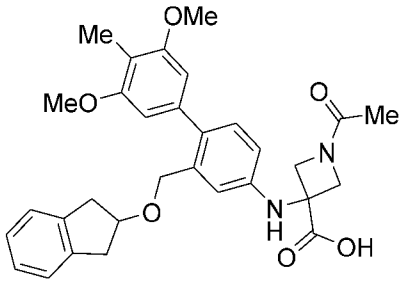
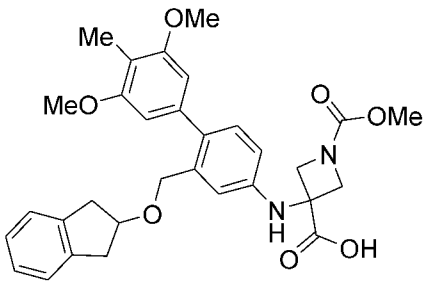
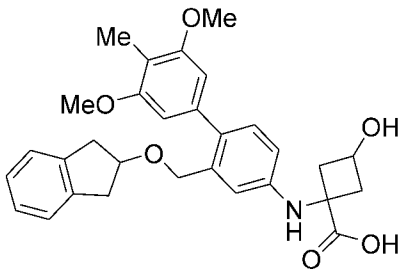
Compound	Structure
101	
102	
103	
104	
105	

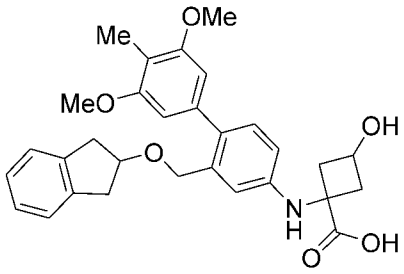
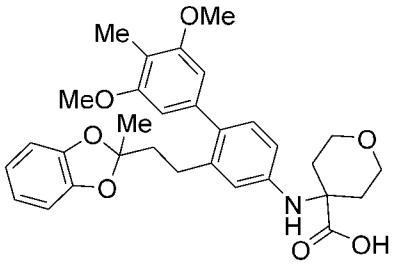
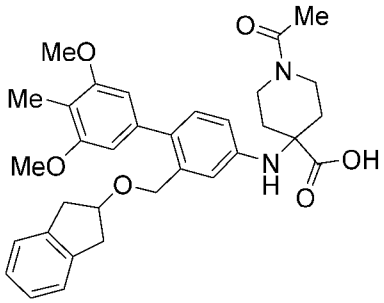
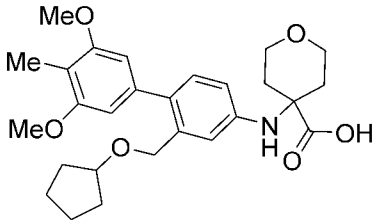
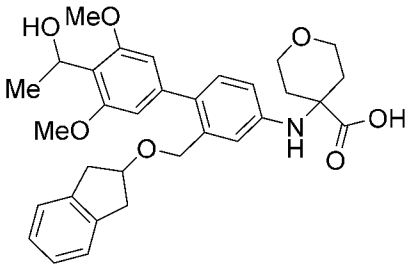
Compound	Structure
106	
107	
108	
109	
110	

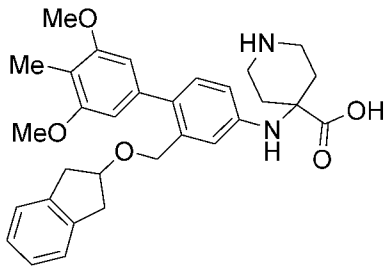
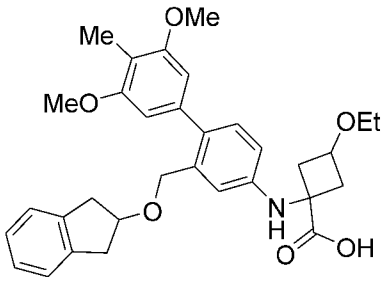
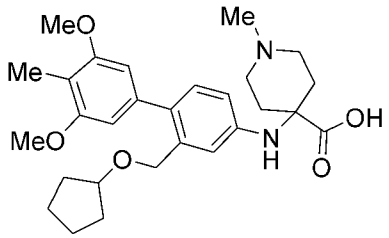
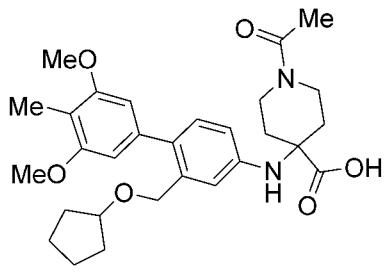
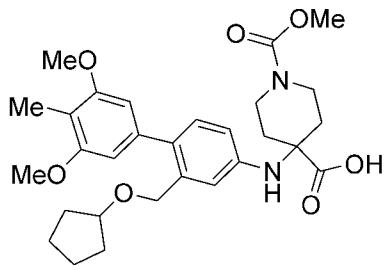
Compound	Structure
111	
112	
113	
114	
115	
116	

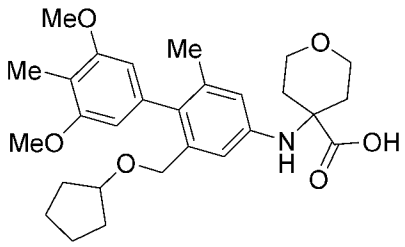
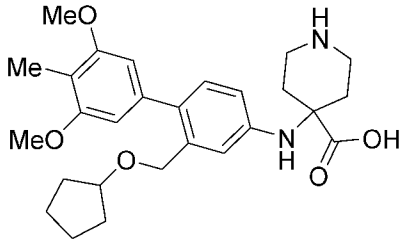
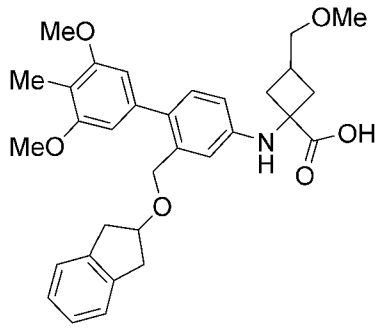
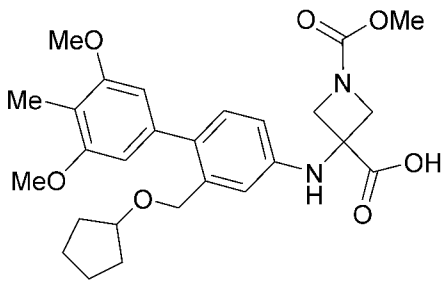
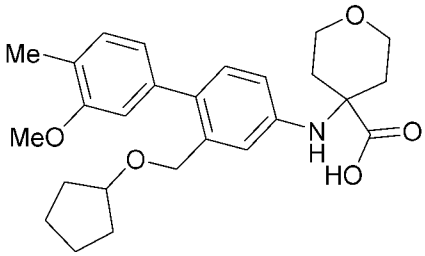
Compound	Structure
117	
118	
119	
120	
121	

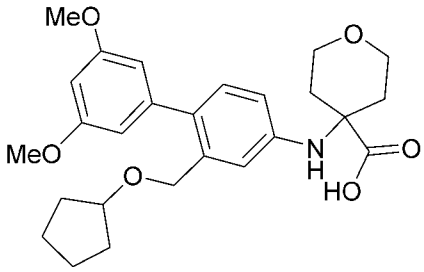
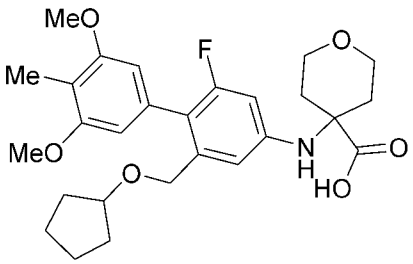
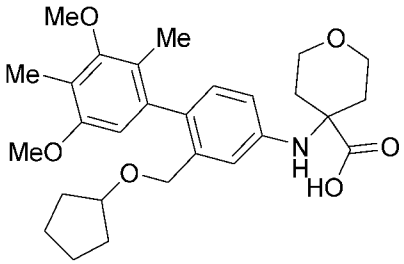
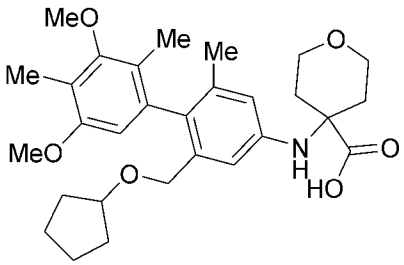
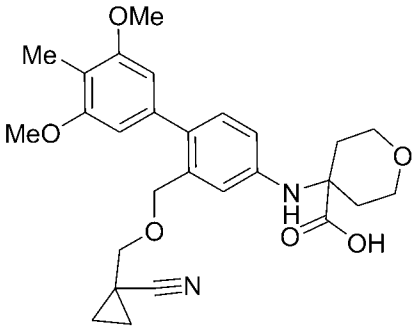
Compound	Structure
122	
123	
124	
125	 Enantiomer 1

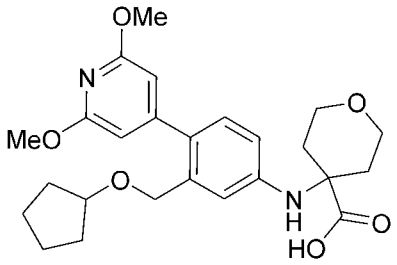
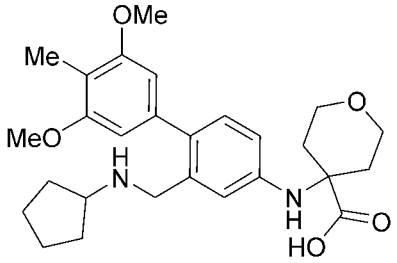
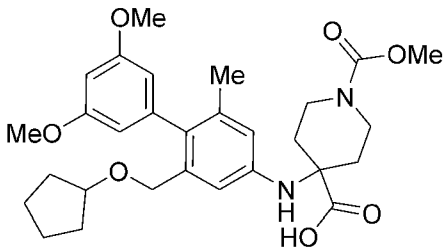
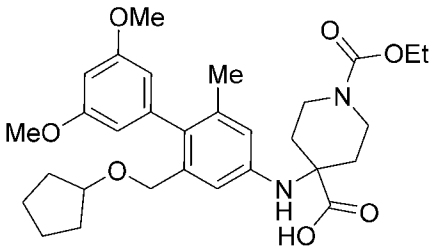
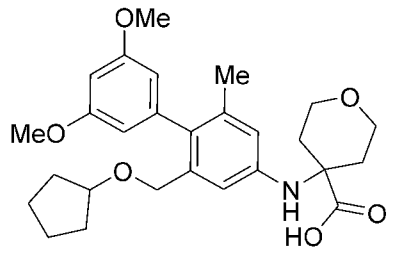
Compound	Structure
126	 Enantiomer 2
127	
128	
129	
130	 Enantiomer 1

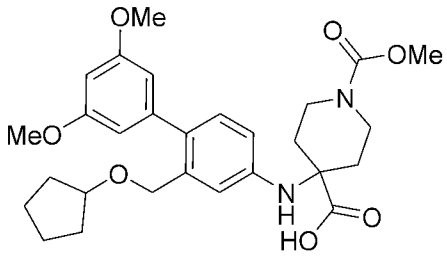
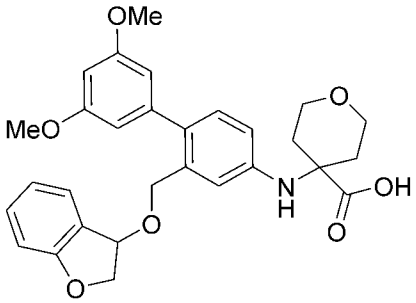
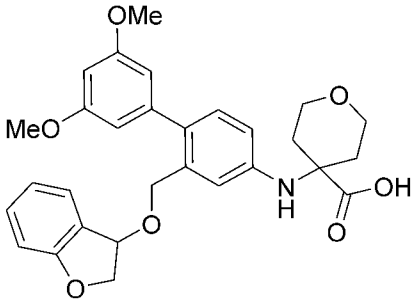
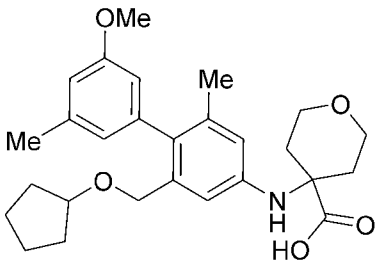
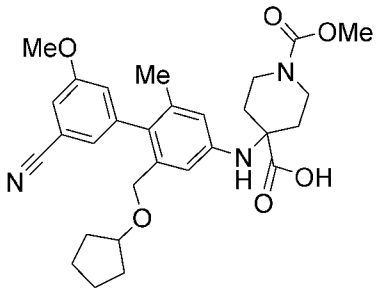
Compound	Structure
131	 Enantiomer 2
132	
133	
134	
135	

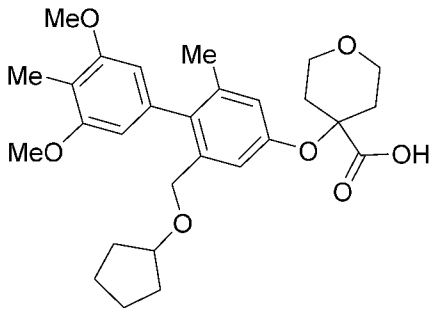
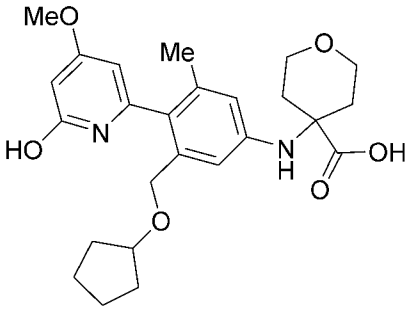
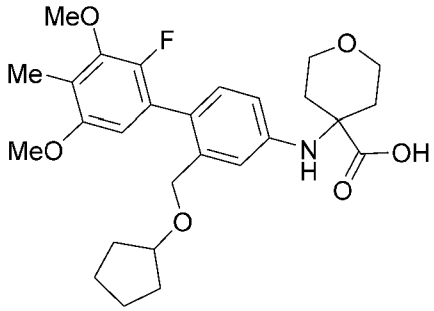
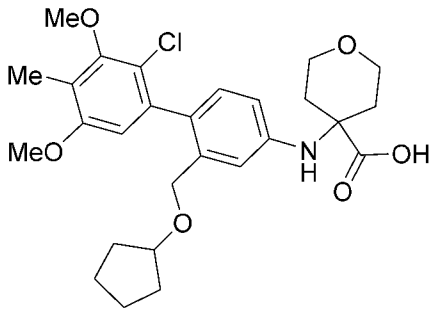
Compound	Structure
136	
137	
138	
139	
140	

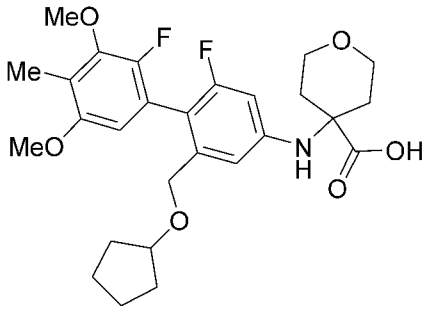
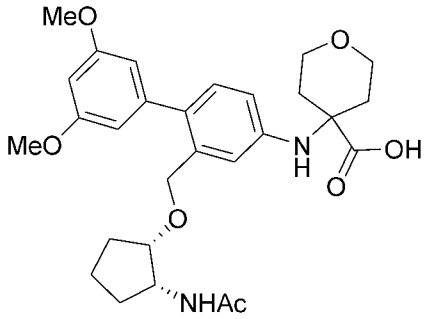
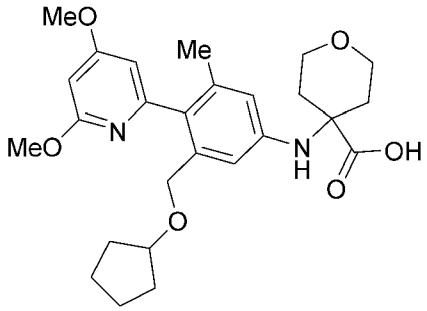
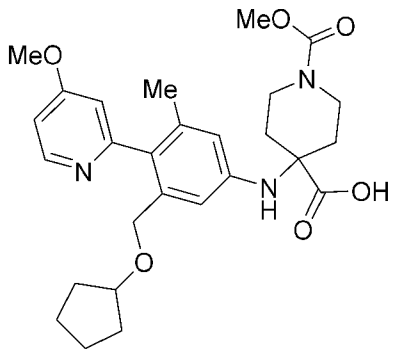
Compound	Structure
141	
142	
143	
144	
145	

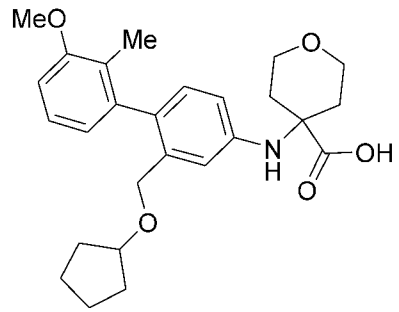
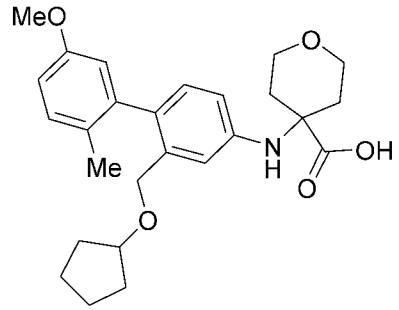
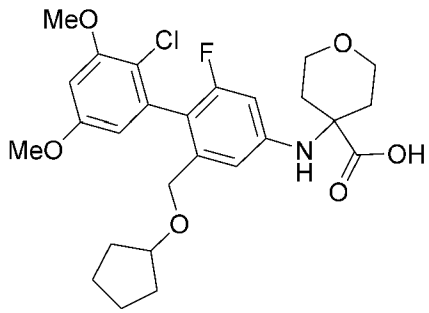
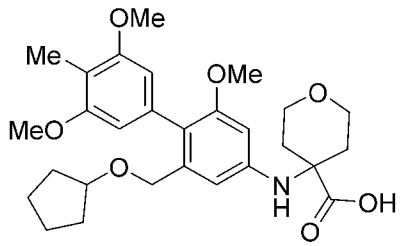
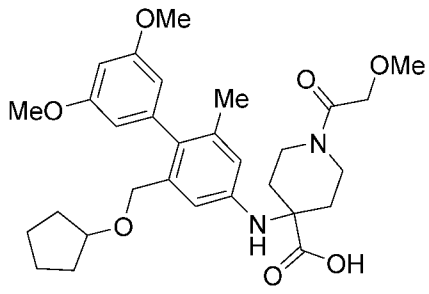
Compound	Structure
146	
147	
148	
149	
151	

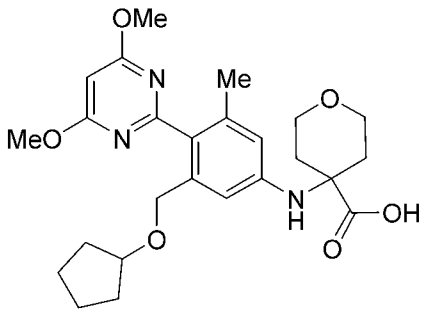
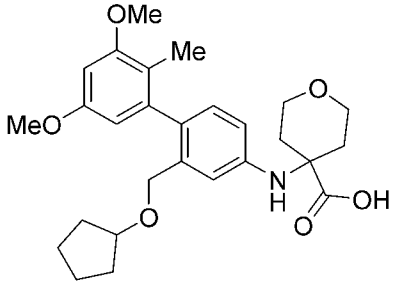
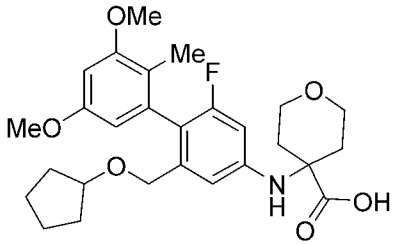
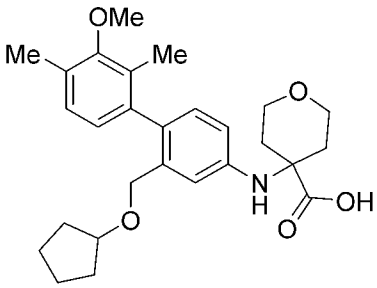
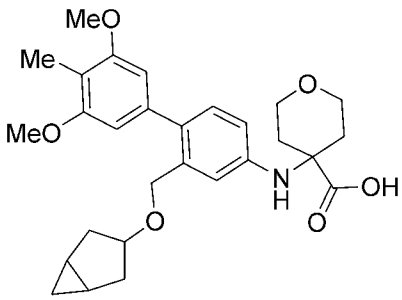
Compound	Structure
152	
153	
154	
155	
156	

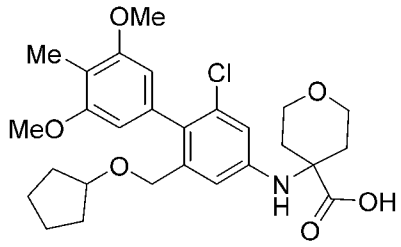
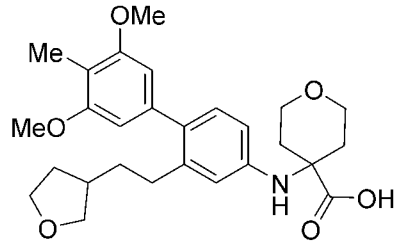
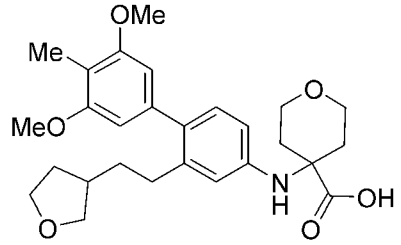
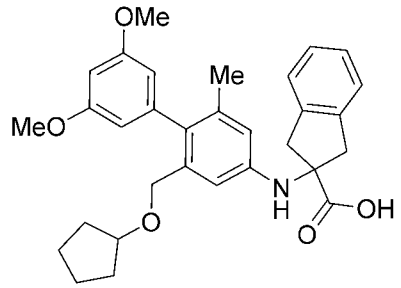
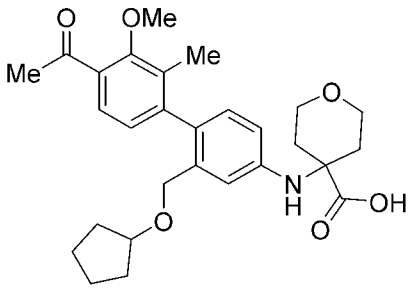
Compound	Structure
157	
158	 Enantiomer 1
159	 Enantiomer 2
160	
161	

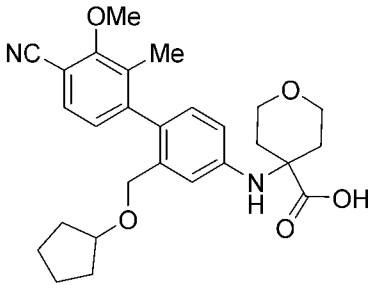
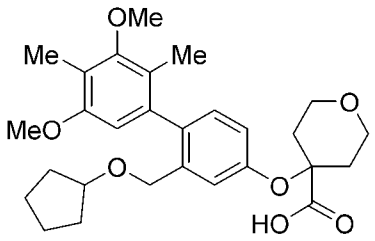
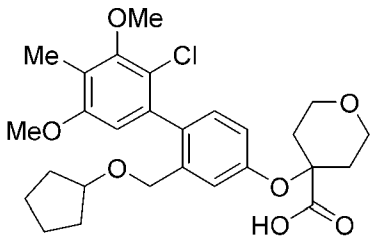
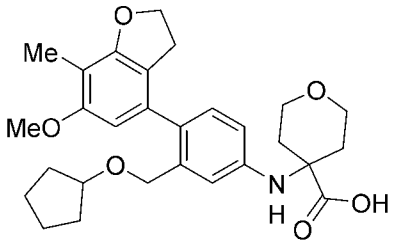
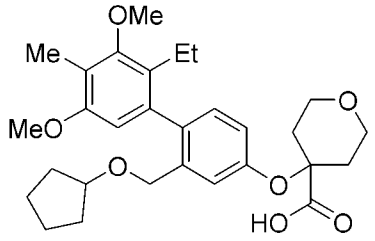
Compound	Structure
163	
164	
165	
166	

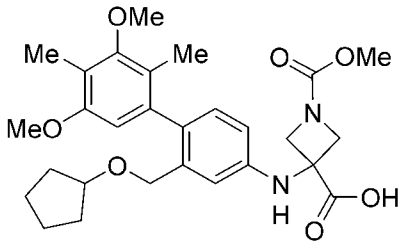
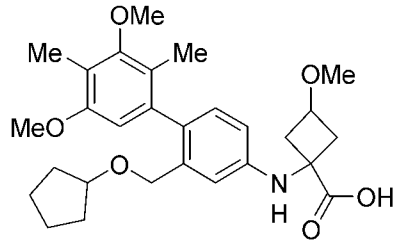
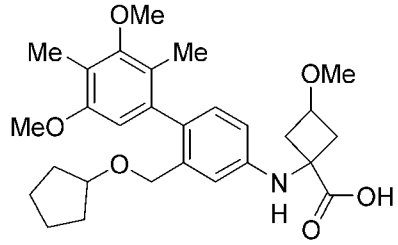
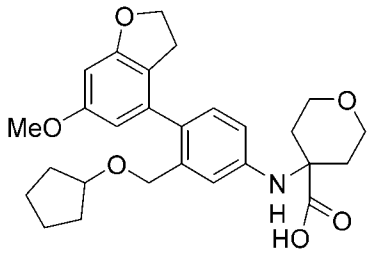
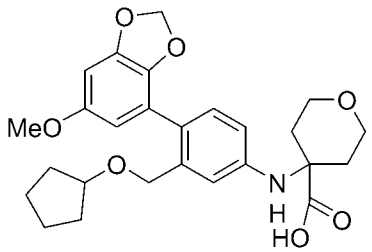
Compound	Structure
168	
169	
170	
171	

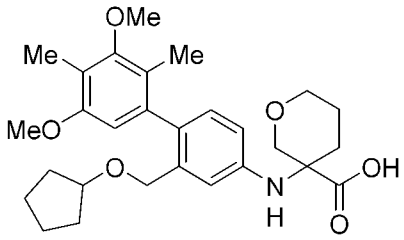
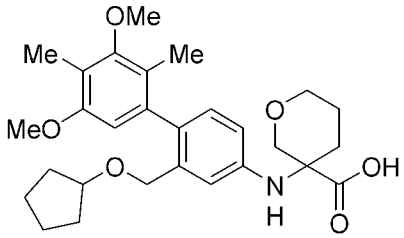
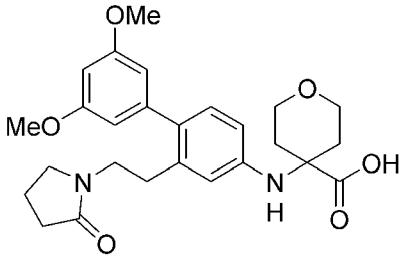
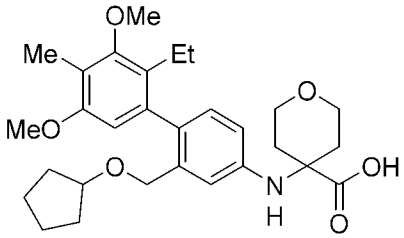
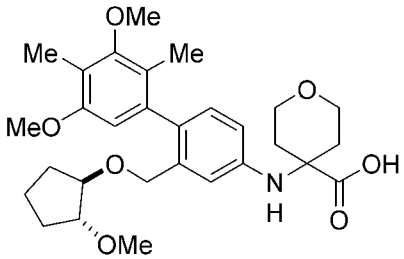
Compound	Structure
172	
173	
174	
175	
176	

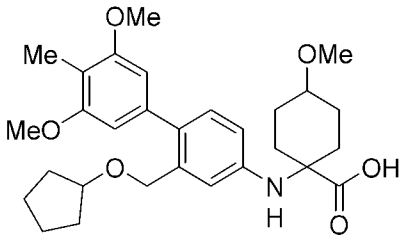
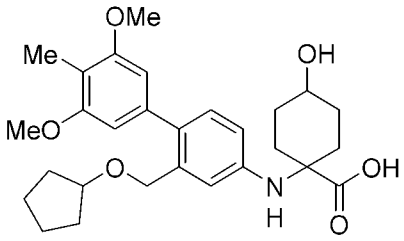
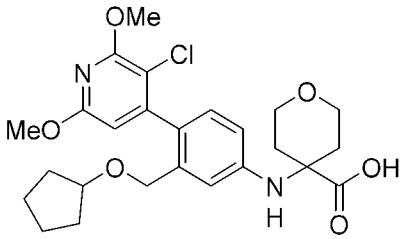
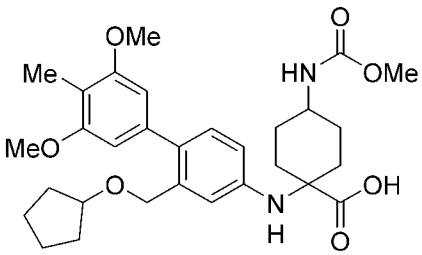
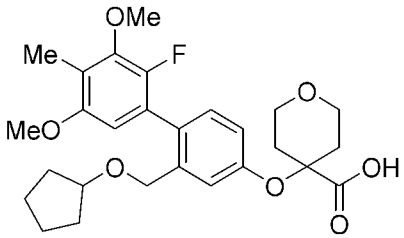
Compound	Structure
178	
179	
180	
181	
182	

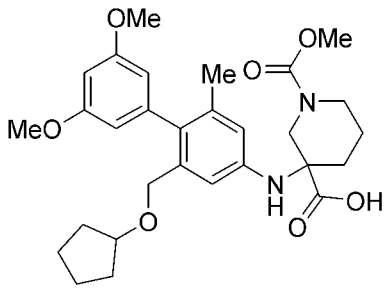
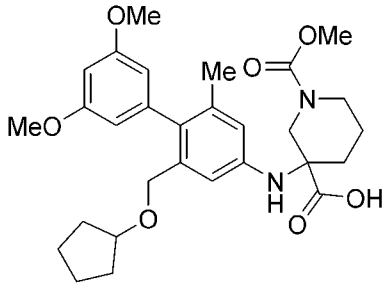
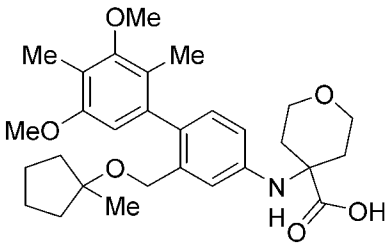
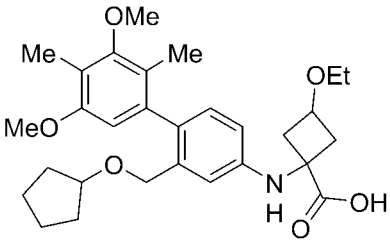
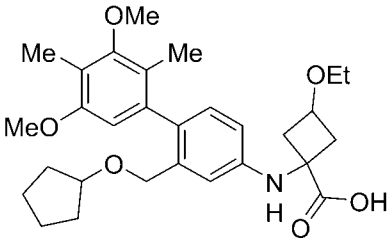
Compound	Structure
184	
185	 Enantiomer 1
186	 Enantiomer 2
188	
189	

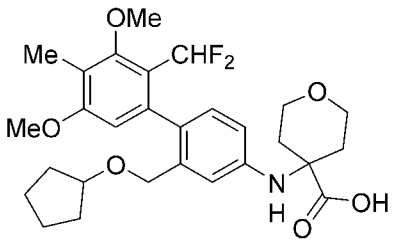
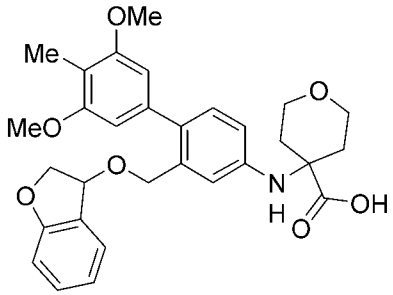
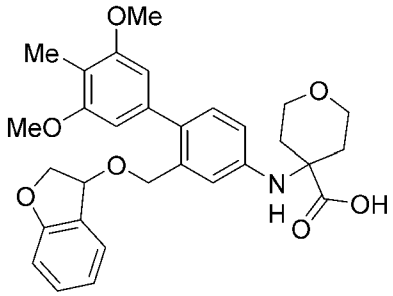
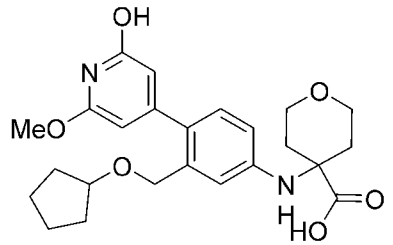
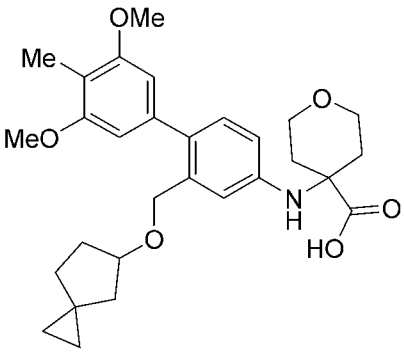
Compound	Structure
190	
191	
192	
193	
194	

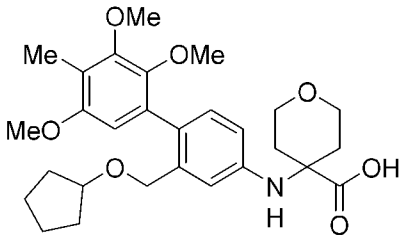
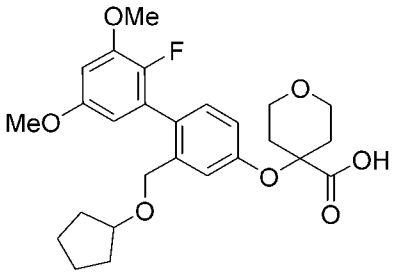
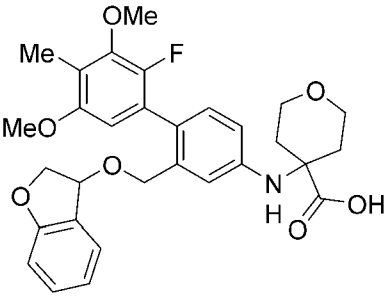
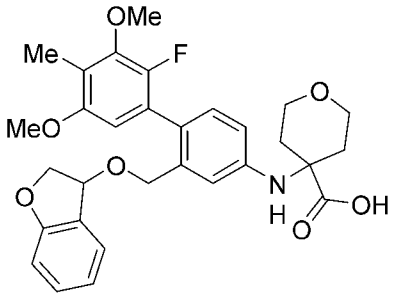
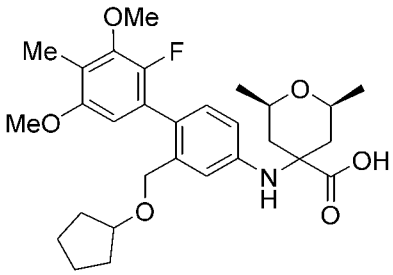
Compound	Structure
195	
196	 Enantiomer 1
197	 Enantiomer 2
198	
199	

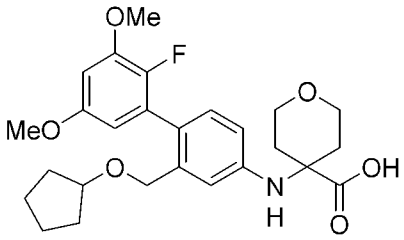
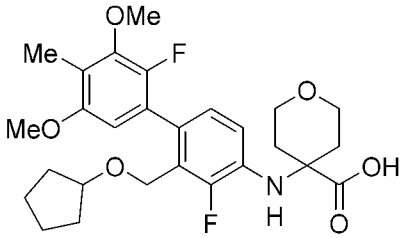
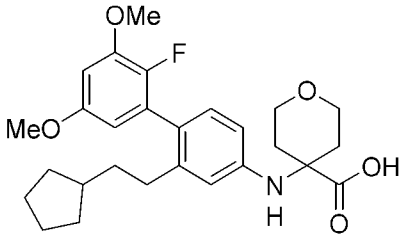
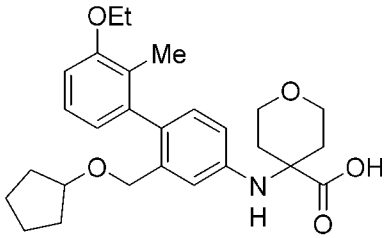
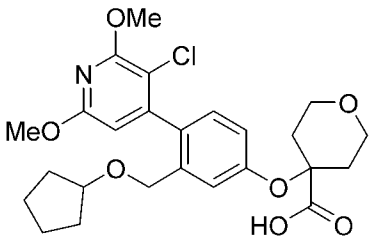
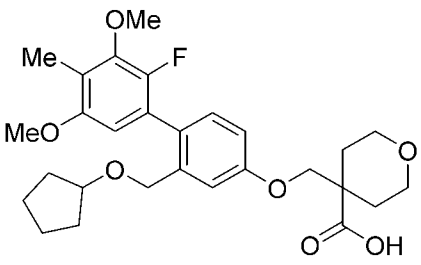
Compound	Structure
200	 Enantiomer 1
201	 Enantiomer 2
202	
203	
204	 Trans (mixture of enantiomers)

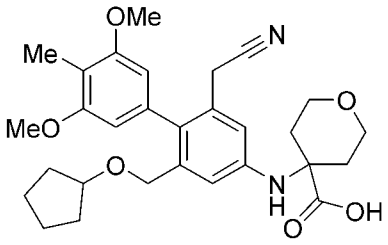
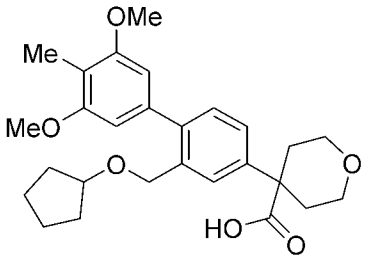
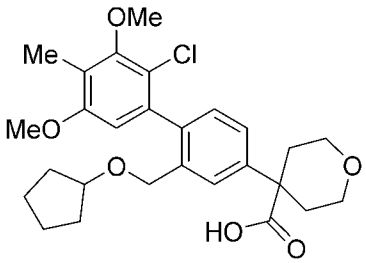
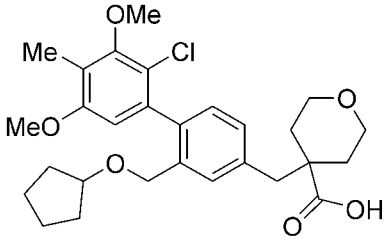
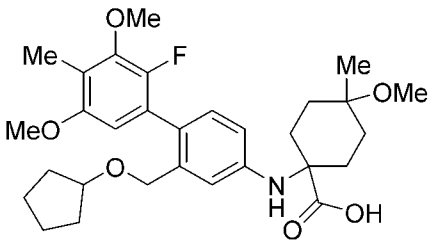
Compound	Structure
205	
206	
207	
208	
209	

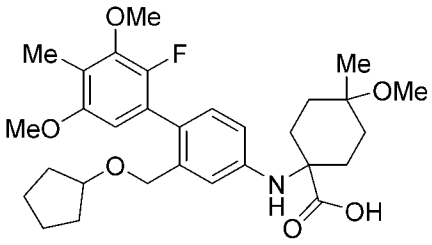
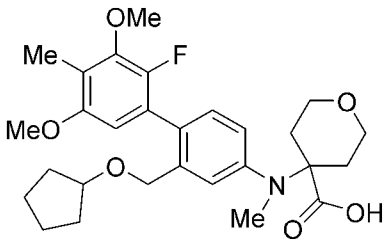
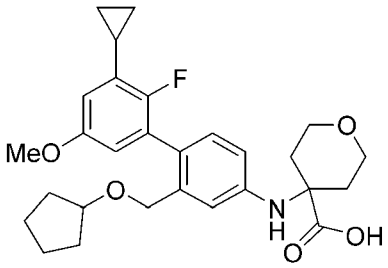
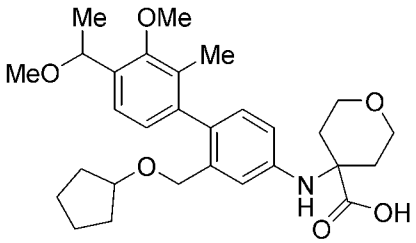
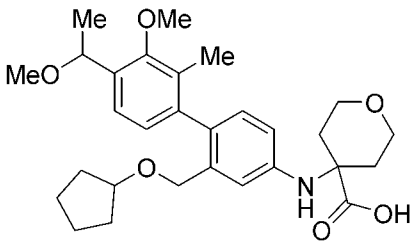
Compound	Structure
210	 Enantiomer 1
211	 Enantiomer 2
212	
213	 Enantiomer 1
214	 Enantiomer 2

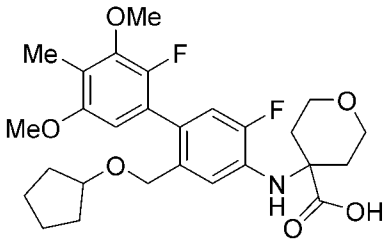
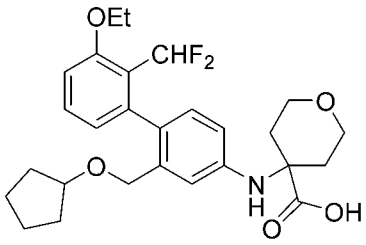
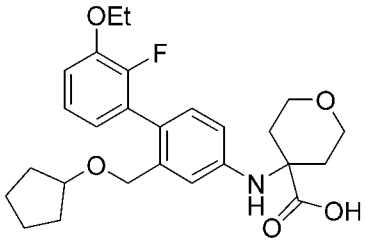
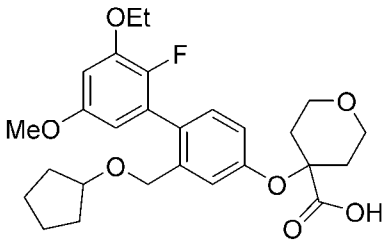
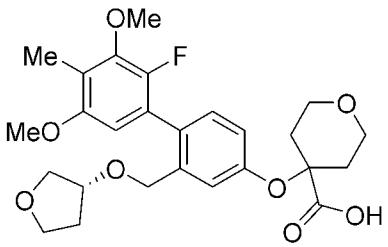
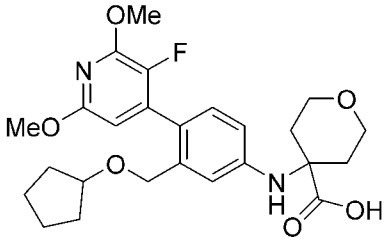
Compound	Structure
215	
216	 Enantiomer 1
217	 Enantiomer 2
218	
219	

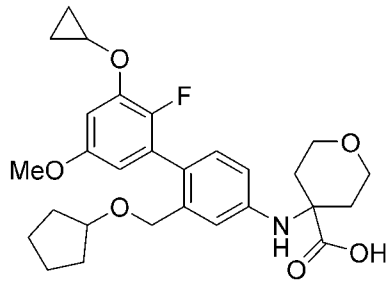
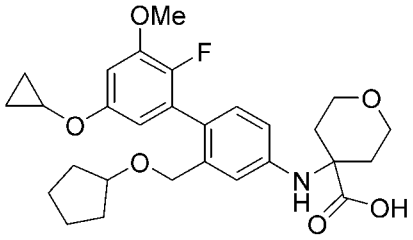
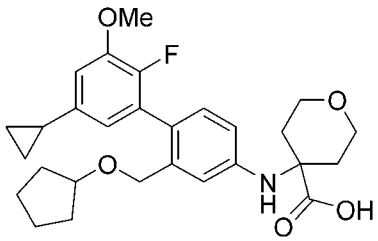
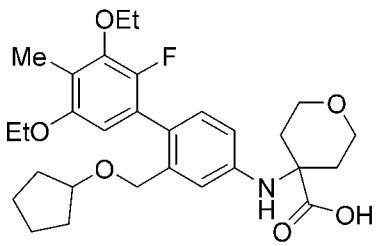
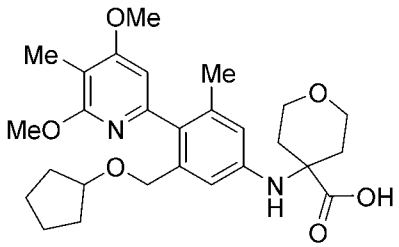
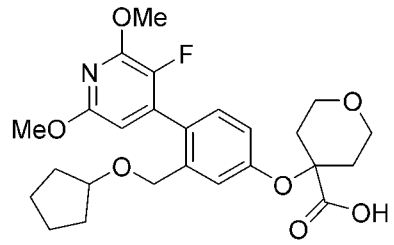
Compound	Structure
220	
222	
223	 Enantiomer 1
224	 Enantiomer 2
225	

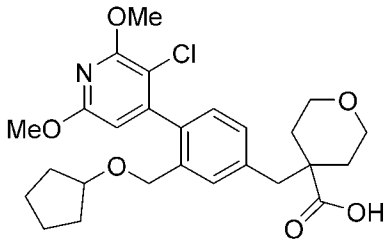
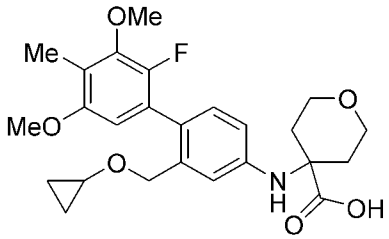
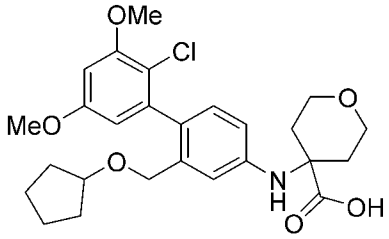
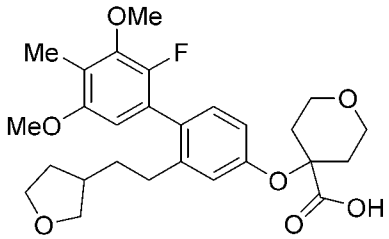
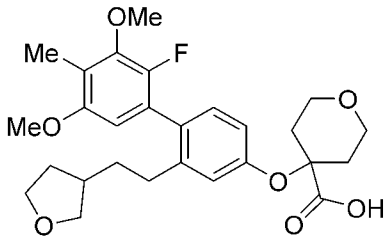
Compound	Structure
226	
227	
228	
229	
230	
232	

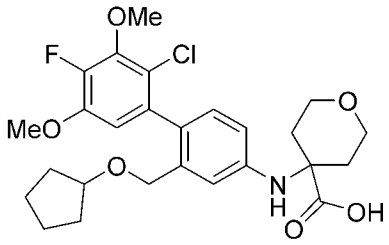
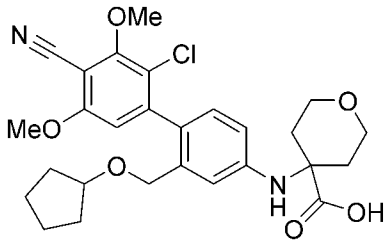
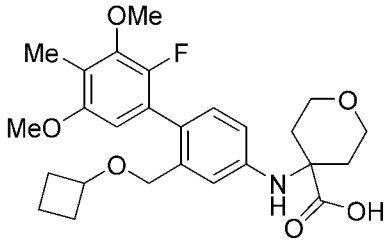
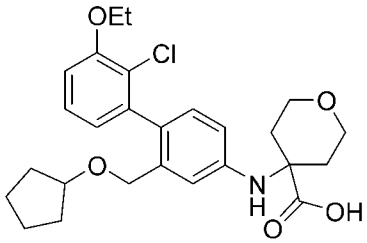
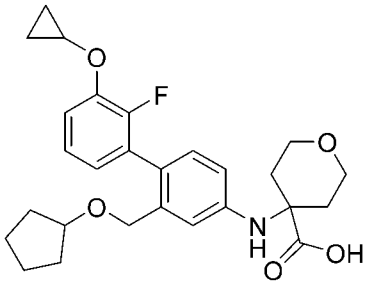
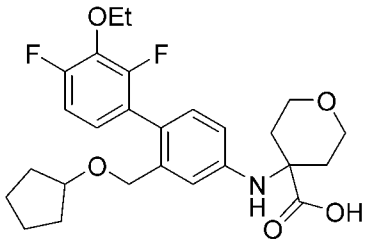
Compound	Structure
233	
234	
235	
236	
237	 Enantiomer 1

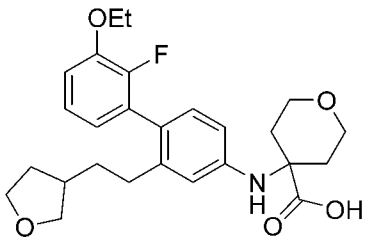
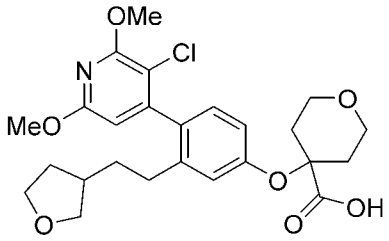
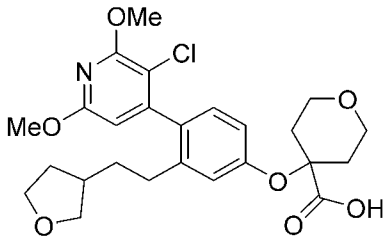
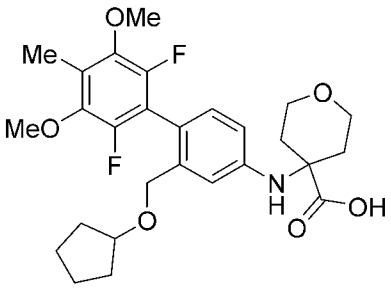
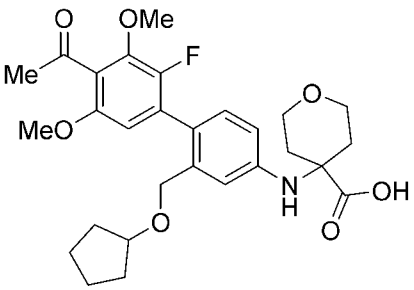
Compound	Structure
238	 Enantiomer 2
239	
240	
241	 Enantiomer 1
242	 Enantiomer 2

Compound	Structure
243	
244	
245	
246	
247	
248	

Compound	Structure
249	
250	
251	
252	
253	
254	

Compound	Structure
255	
256	
257	
259	 Enantiomer 1
260	 Enantiomer 2

Compound	Structure
261	
262	
263	
264	
265	
266	

Compound	Structure
267	
268	 Enantiomer 1
269	 Enantiomer 2
270	
271	

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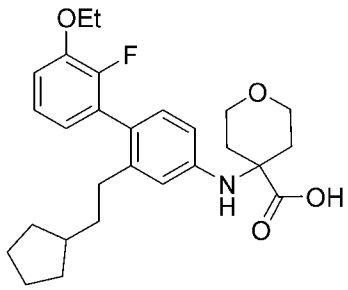
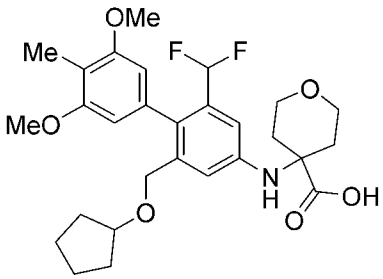
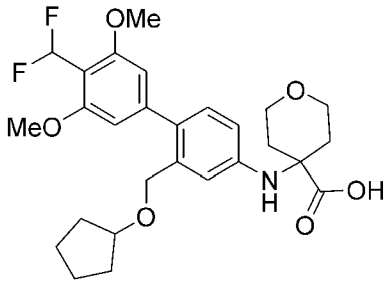
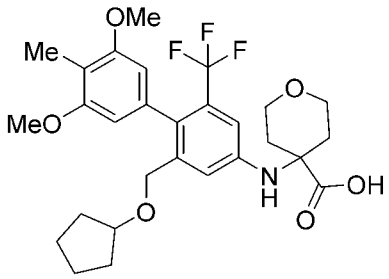
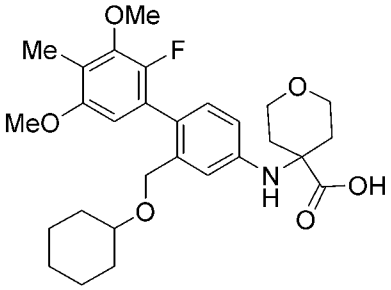
272	
273	
274	
275	
276	

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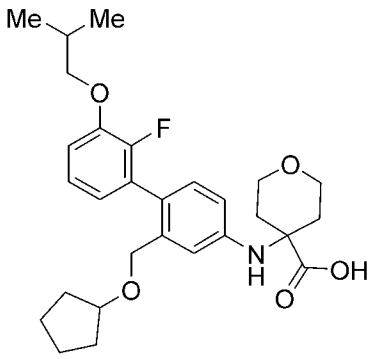
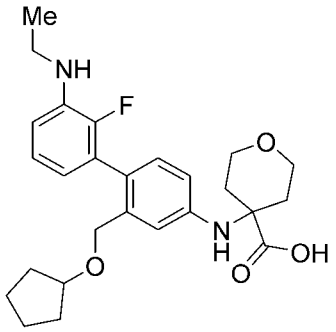
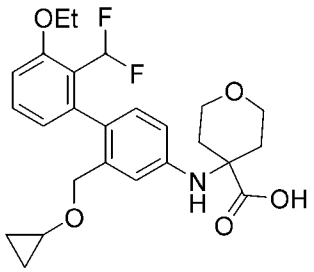
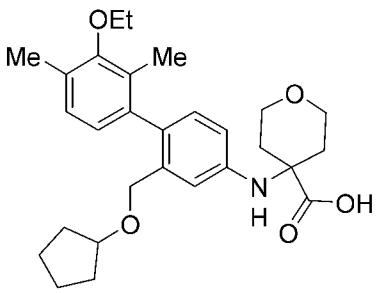
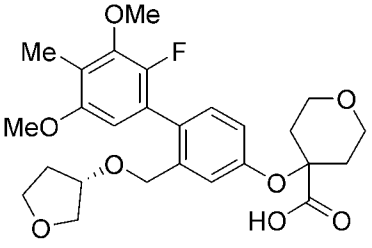
277	
278	
279	
280	
281	

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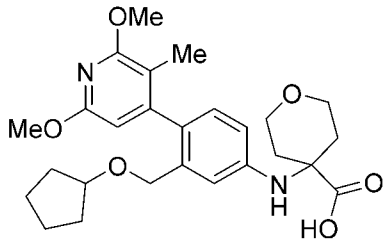
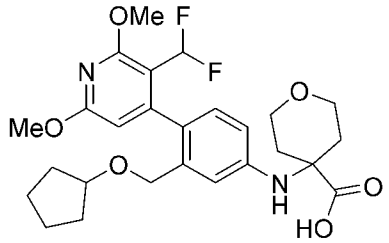
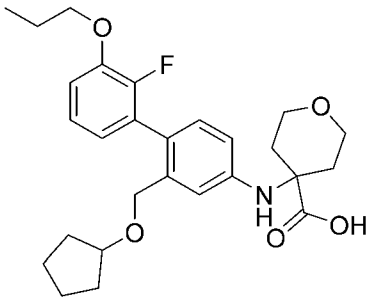
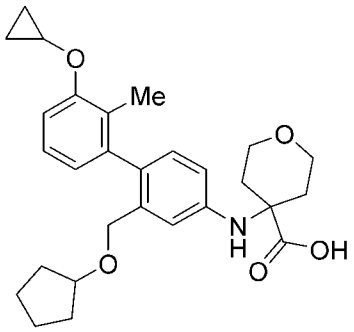
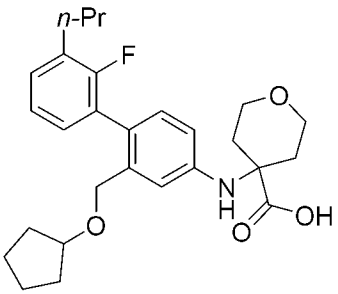
282	
283	
284	
285	
286	

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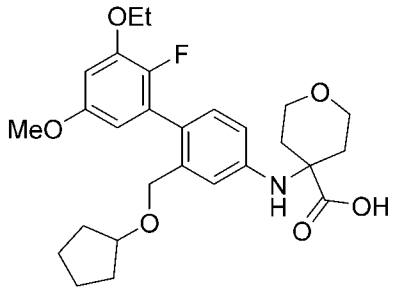
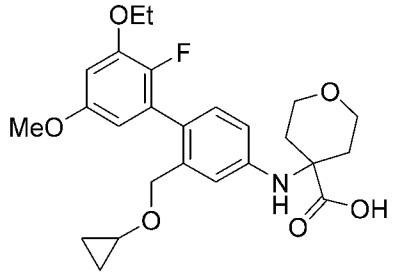
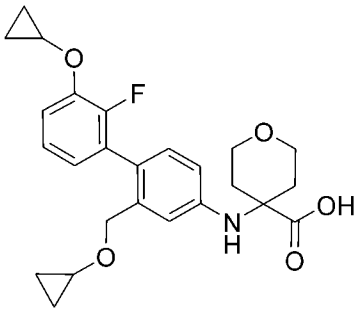
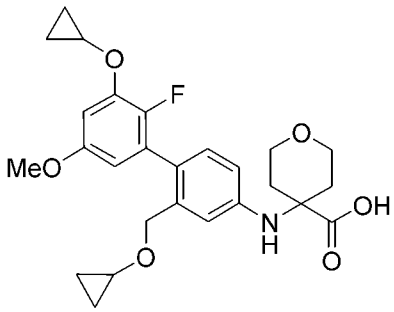
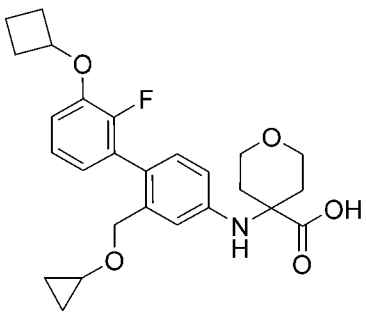
287	
288	
289	
290	
291	

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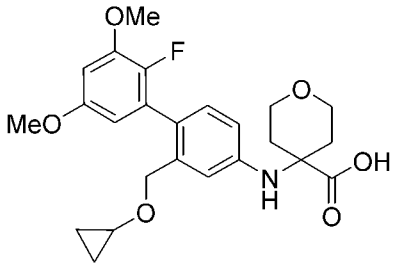
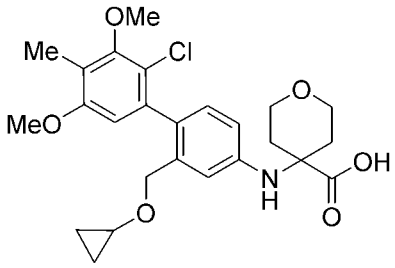
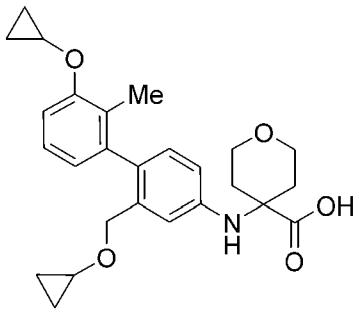
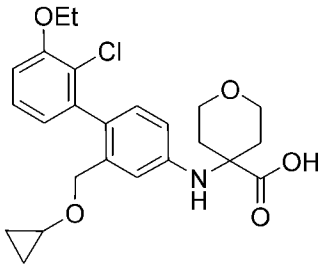
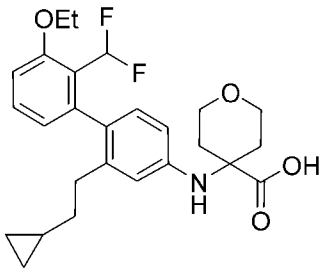
292	
293	
294	
295	
296	

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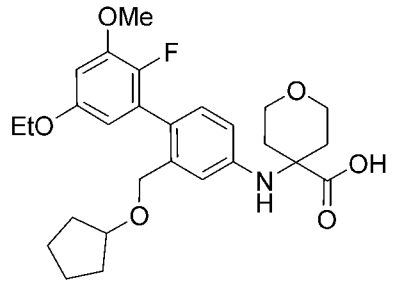
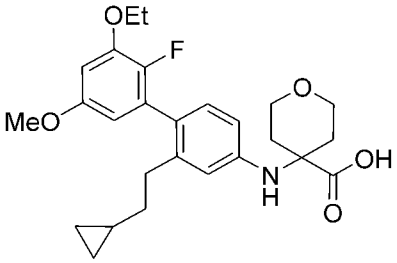
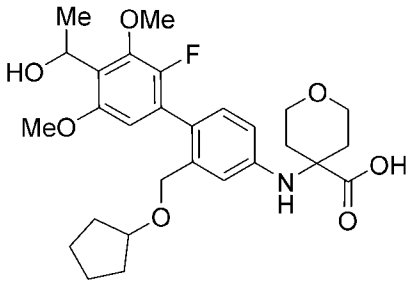
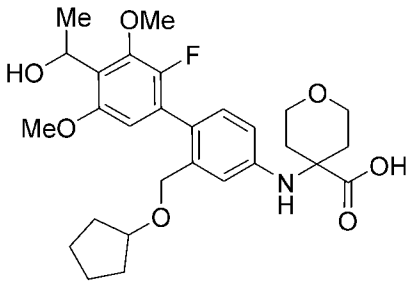
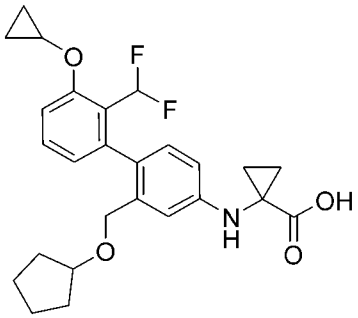
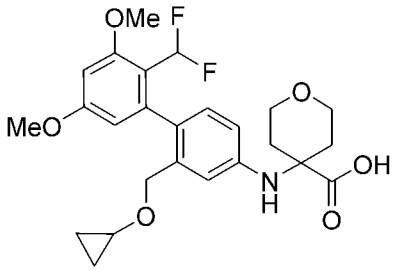
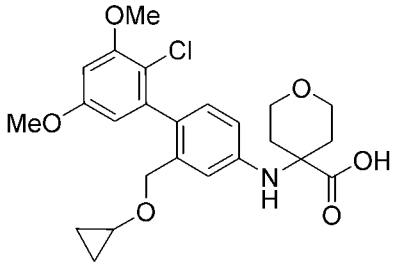
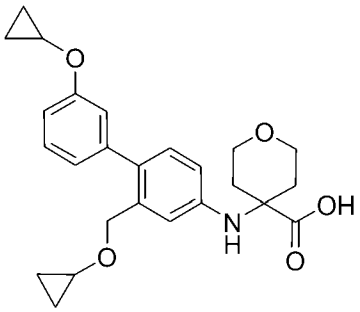
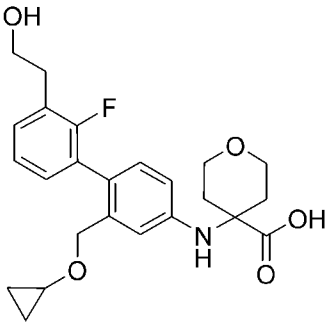
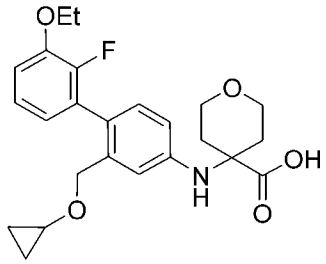
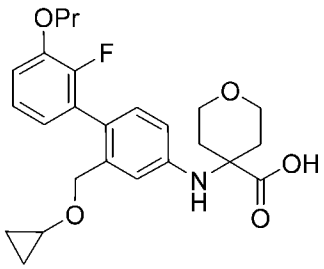
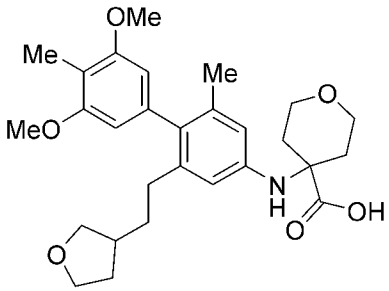
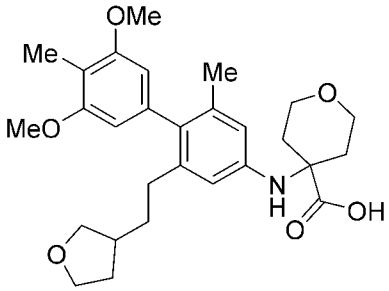
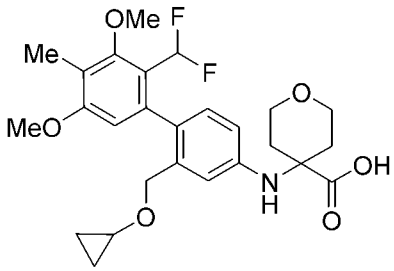
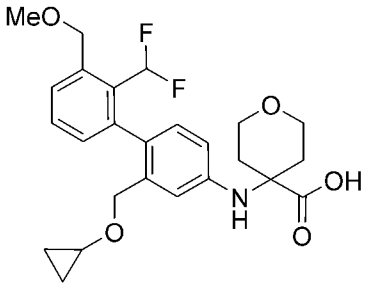
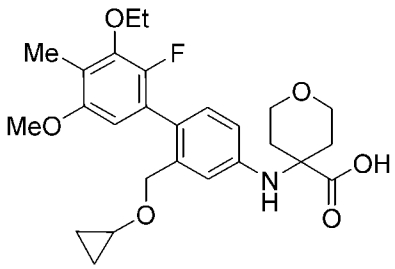
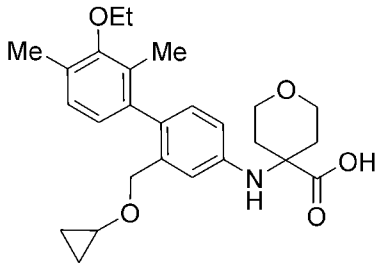
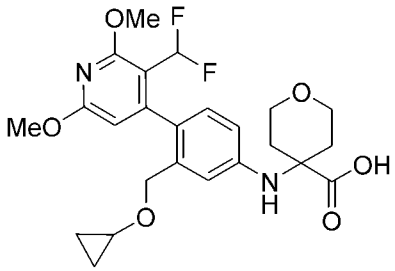
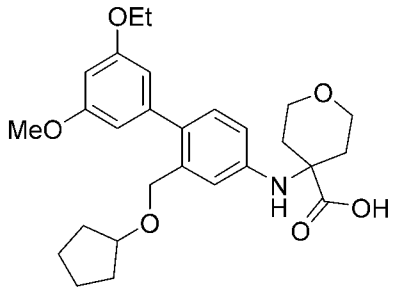
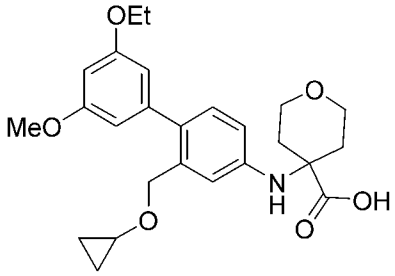
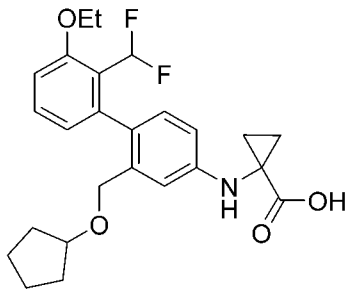
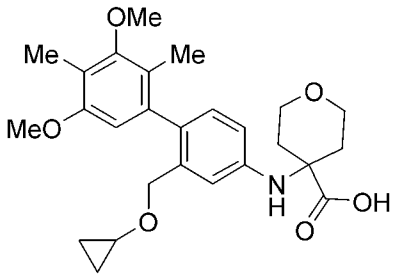
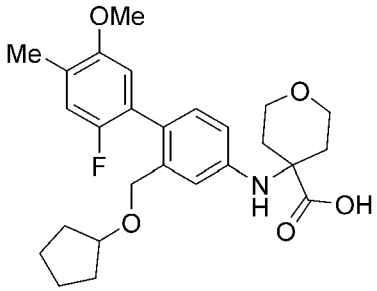
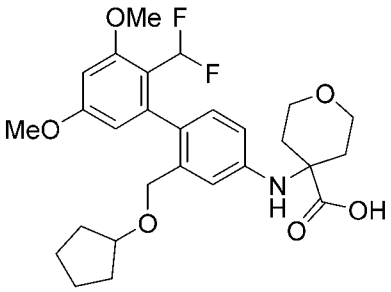
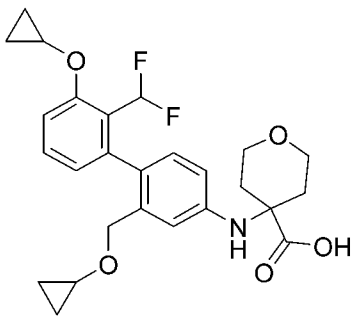
297	
298	
299	 Enantiomer 1
300	 Enantiomer 2
301	

Compound	Structure
302	
303	
304	
305	
306	

Compound	Structure
307	
308	 Enantiomer 1
309	 Enantiomer 2
310	
311	

Compound	Structure
312	
313	
314	
315	
316	

Compound	Structure
317	
318	
319	
320	
322	

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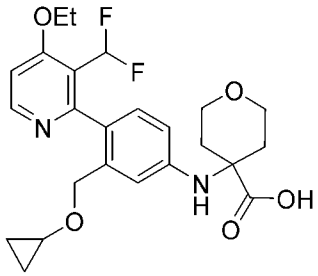
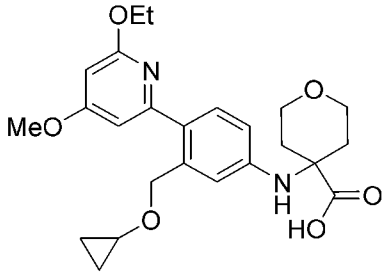
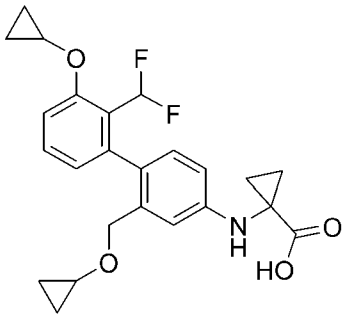
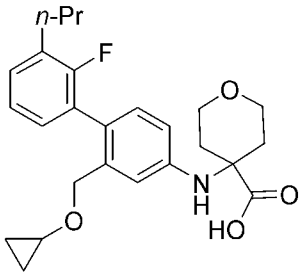
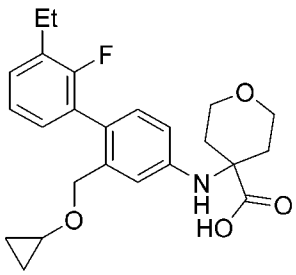
323	
324	
325	
326	
327	

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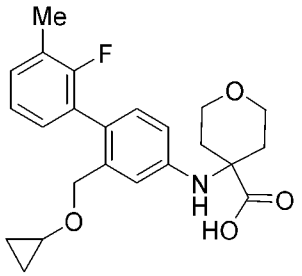
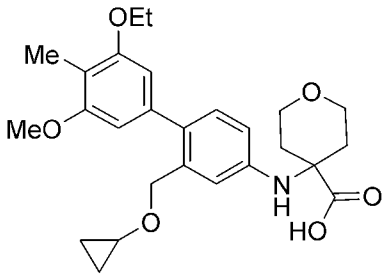
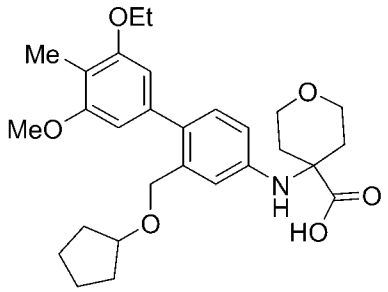
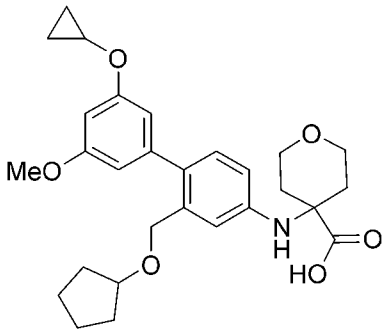
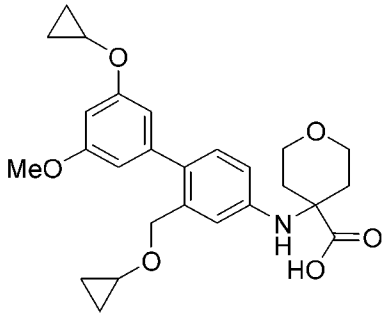
328	
329	
330	
331	
332	

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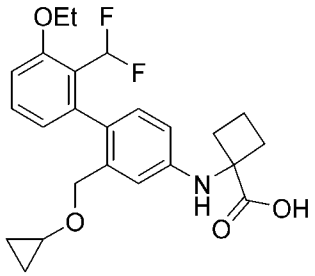
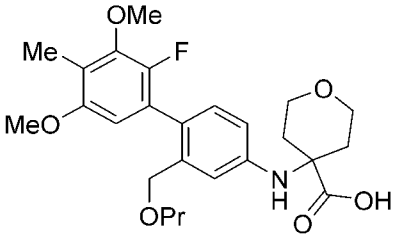
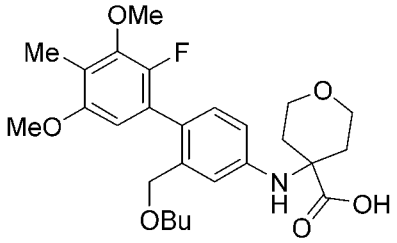
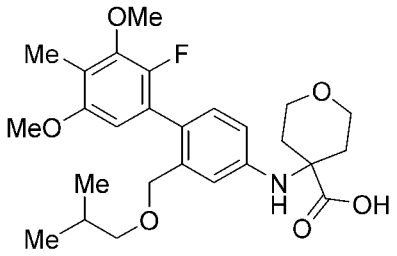
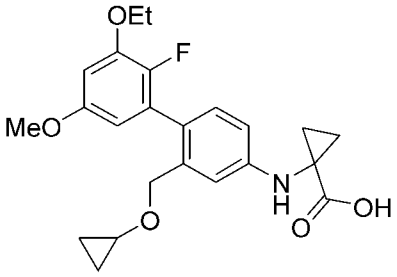
333	
334	
335	
336	
337	

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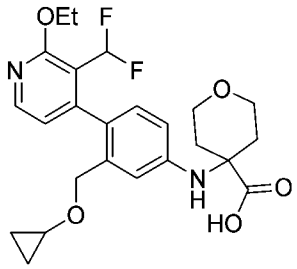
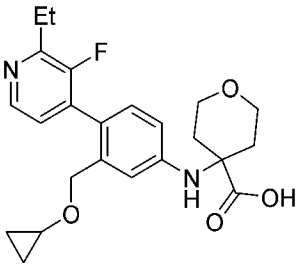
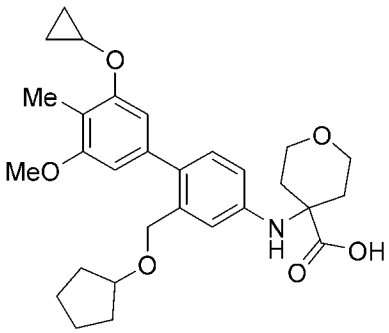
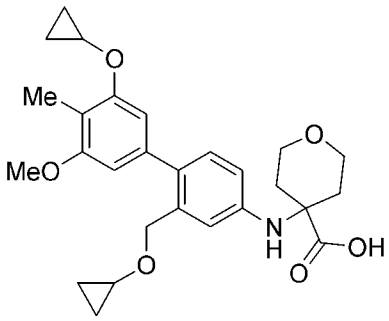
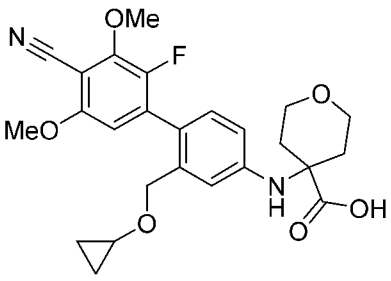
338	
339	
340	
341	
342	

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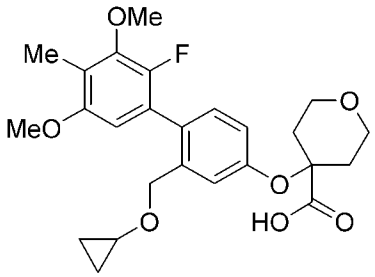
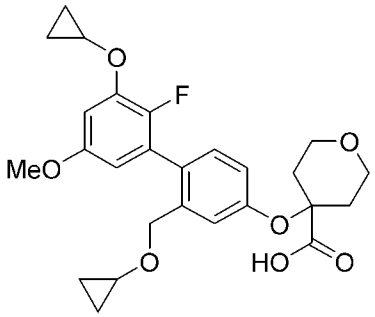
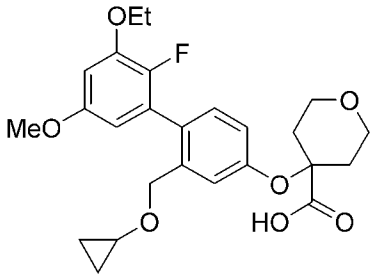
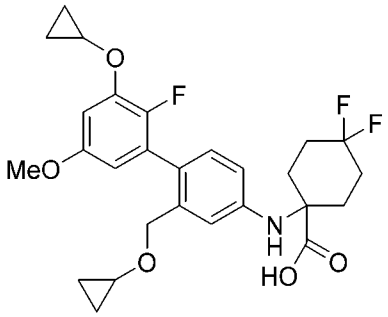
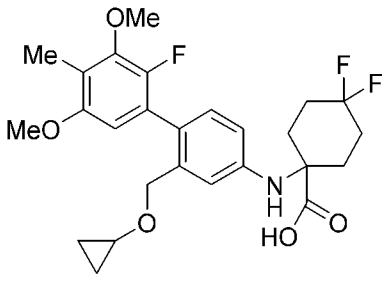
343	
344	
345	
346	
347	

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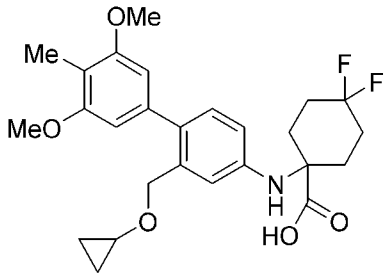
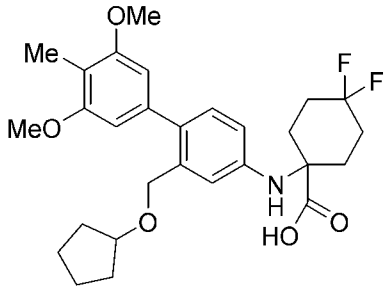
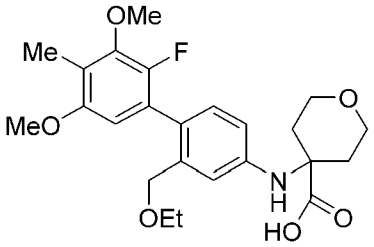
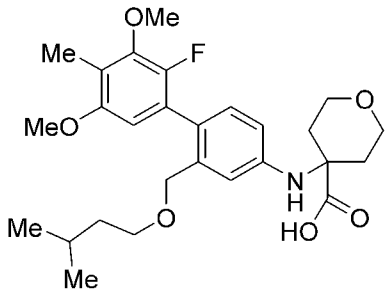
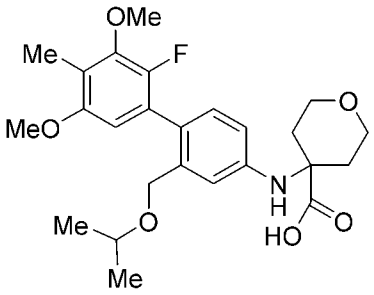
348	
349	
350	
351	
352	

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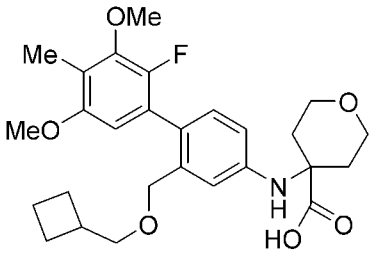
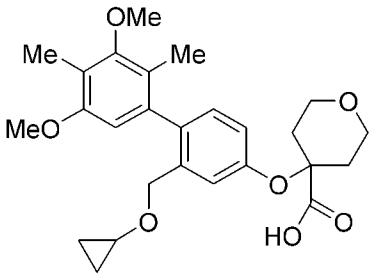
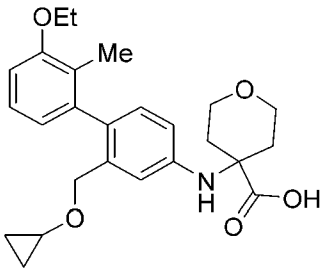
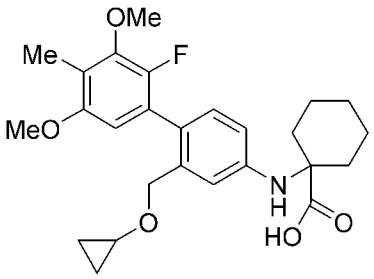
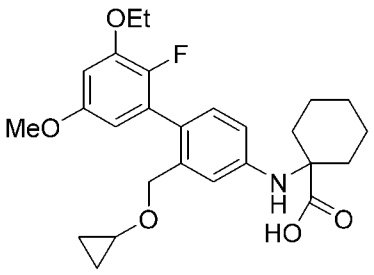
353	
354	
355	
356	
357	

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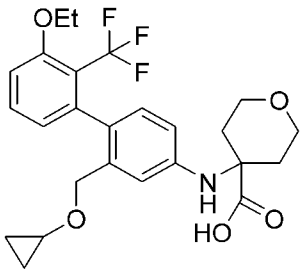
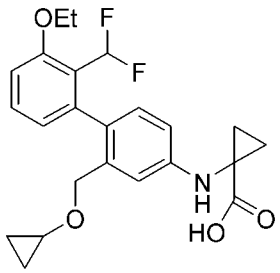
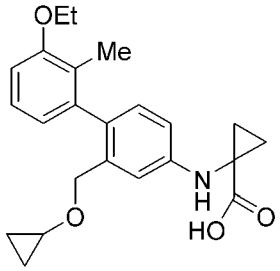
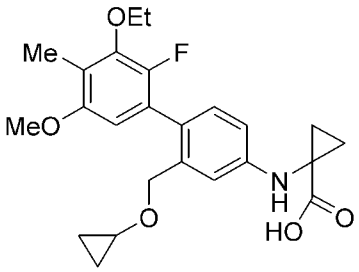
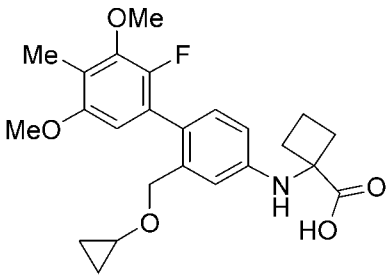
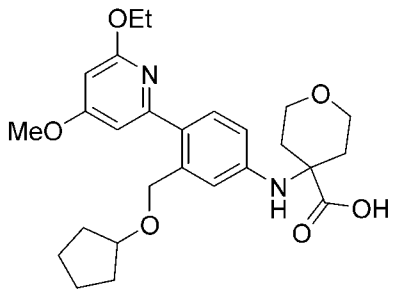
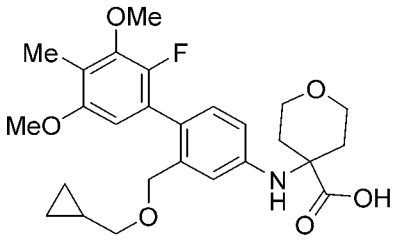
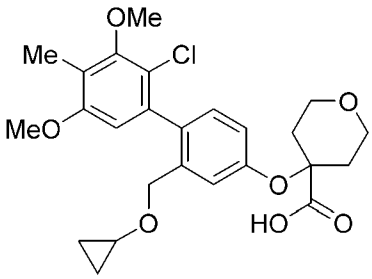
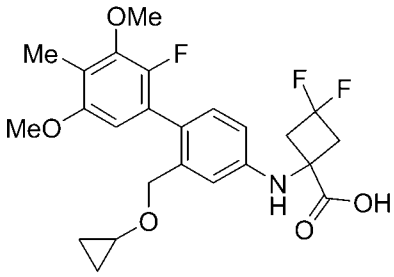
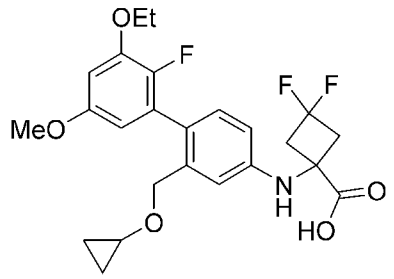
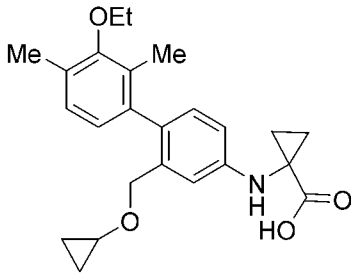
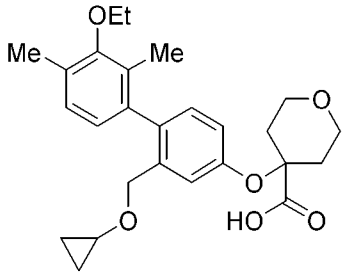
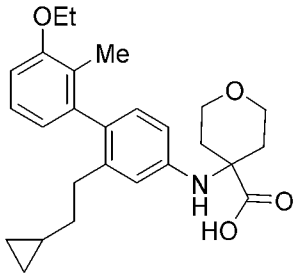
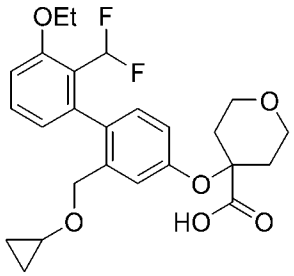
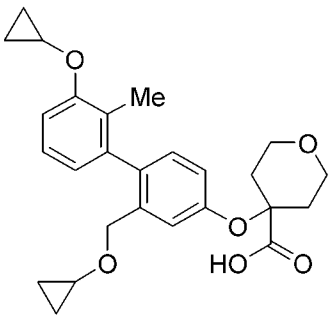
358	
359	
360	
361	
362	

Compound	Structure
363	
364	
365	
366	
367	

Compound	Structure
368	
369	
370	
371	
372	

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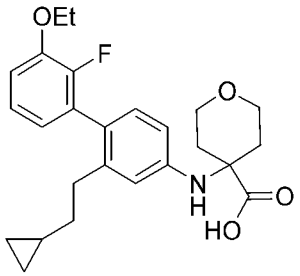
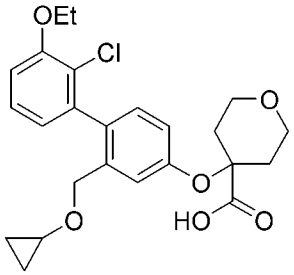
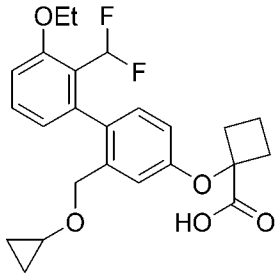
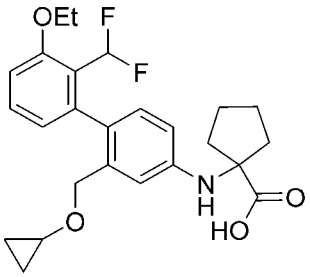
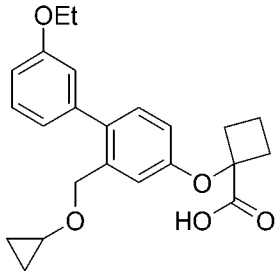
373	
374	
375	
376	
377	

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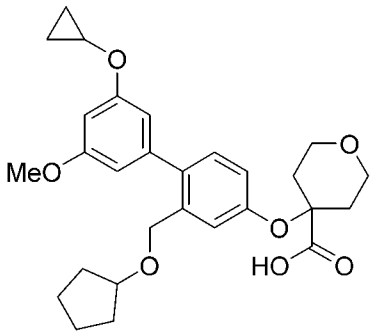
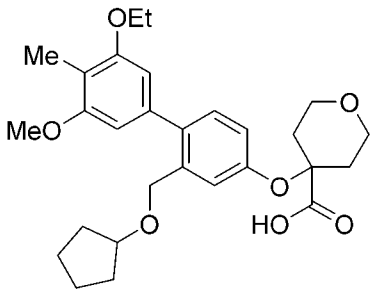
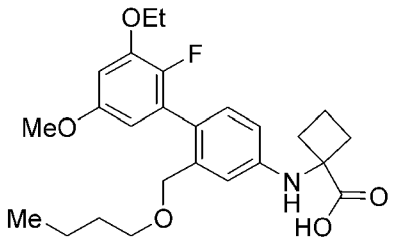
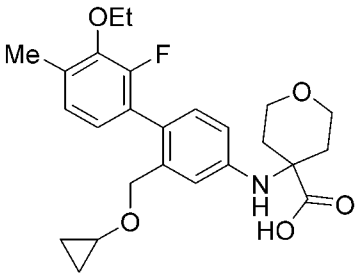
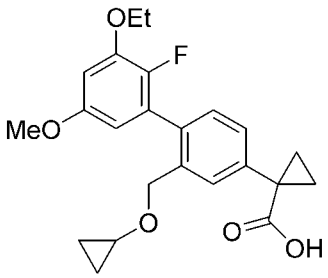
378	
379	
380	
381	
382	

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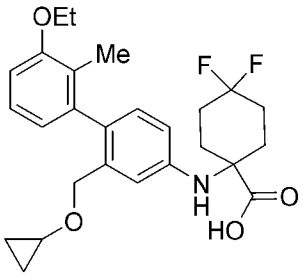
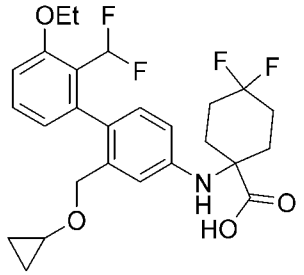
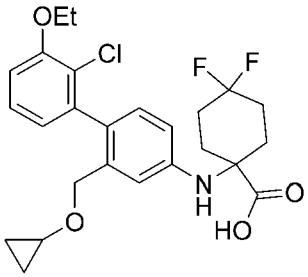
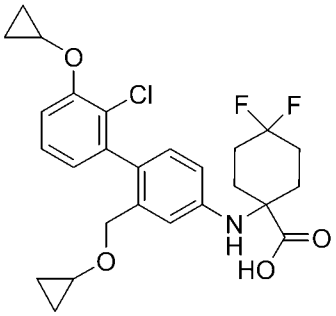
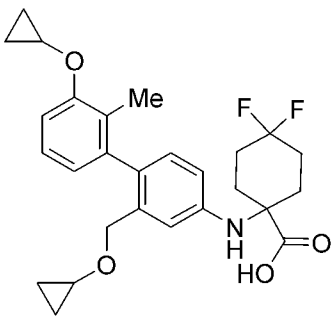
383	
384	
385	
386	
387	

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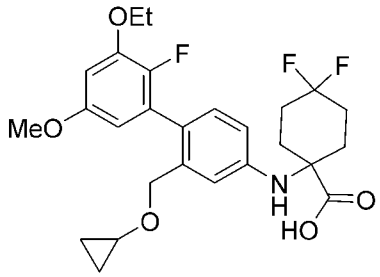
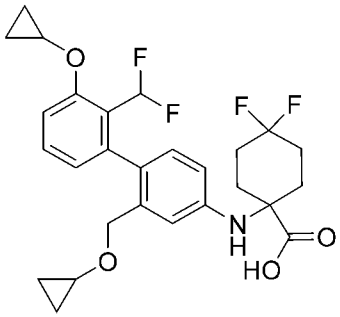
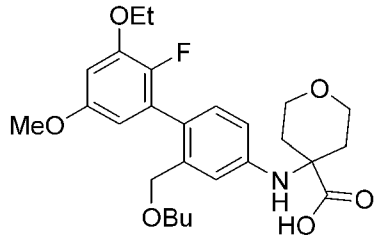
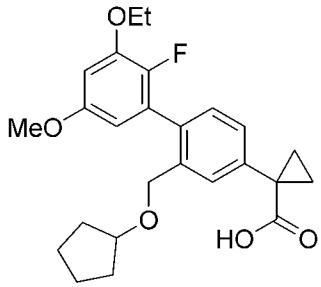
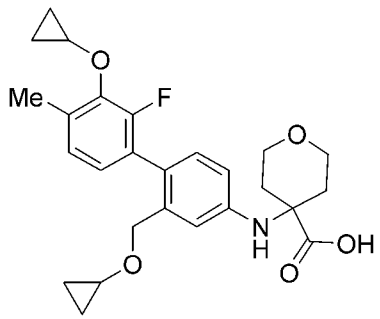
388	
389	
390	
391	
392	

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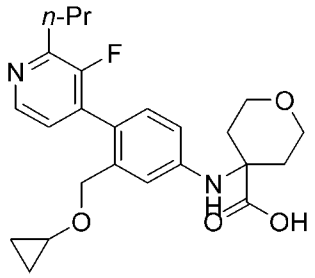
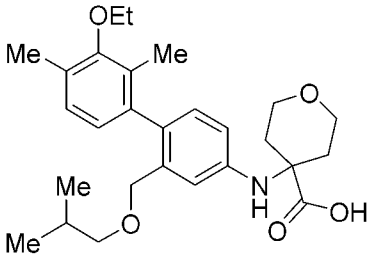
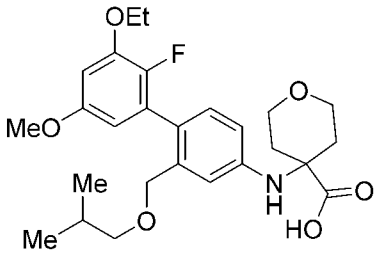
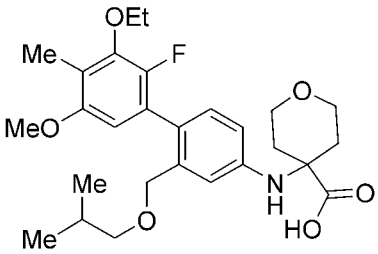
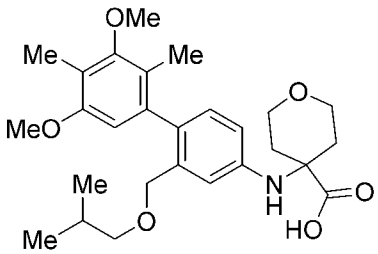
393	
394	
395	
396	
397	

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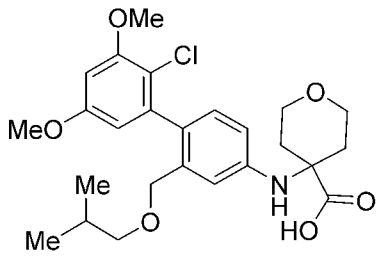
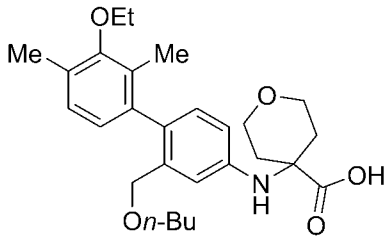
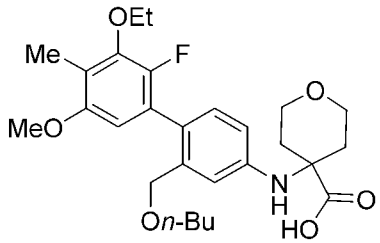
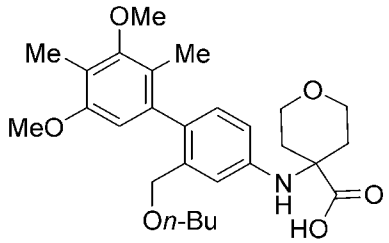
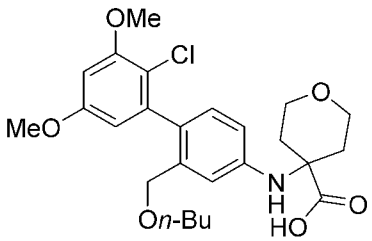
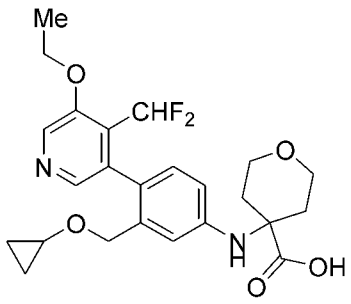
398	
399	
400	
401	
402	
403	

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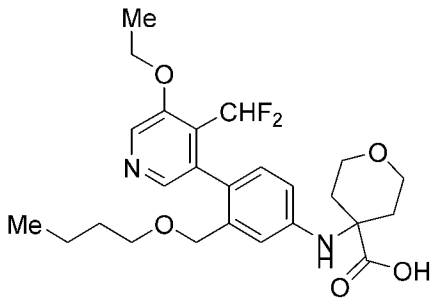
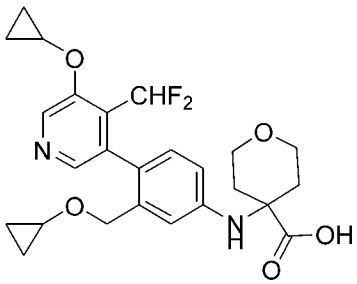
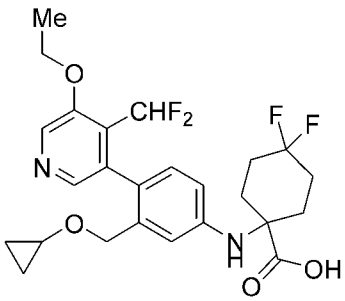
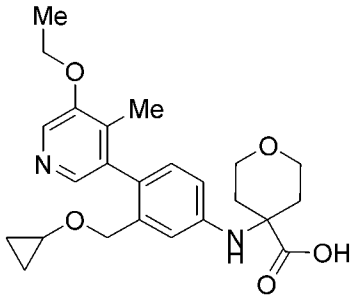
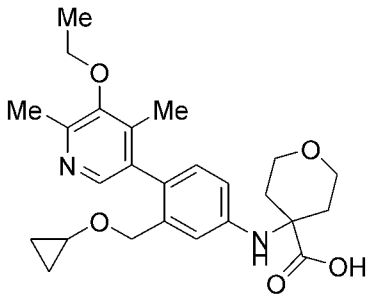
404	
405	
406	
407	
408	

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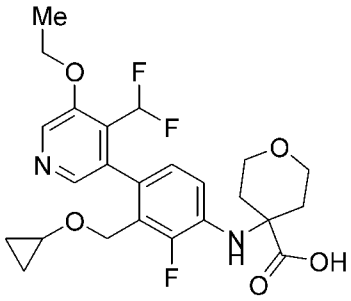
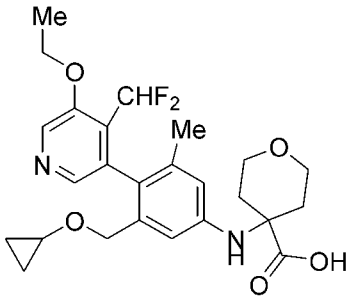
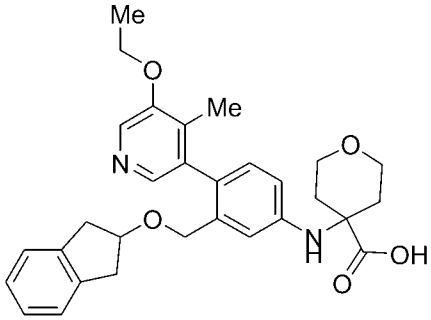
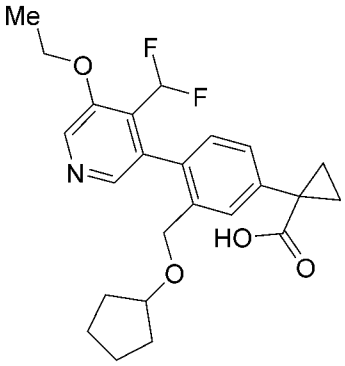
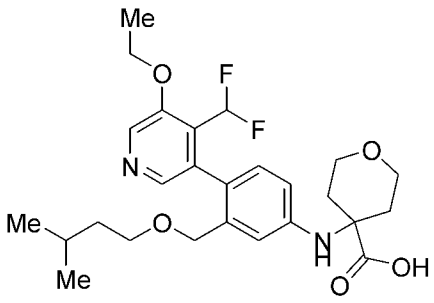
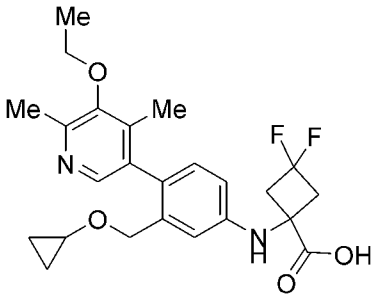
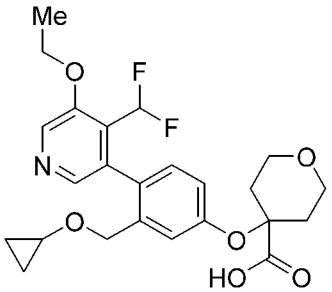
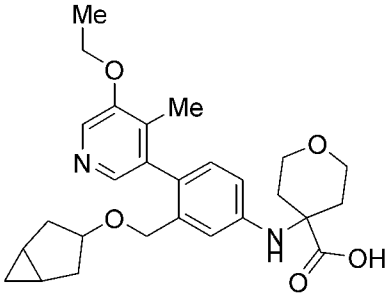
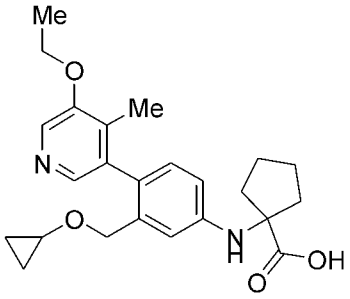
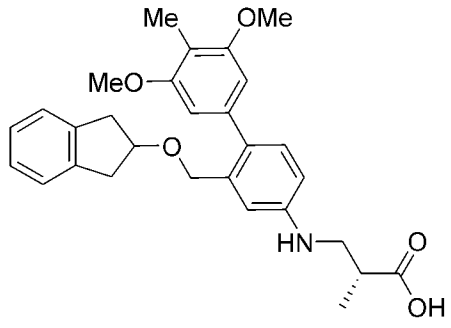
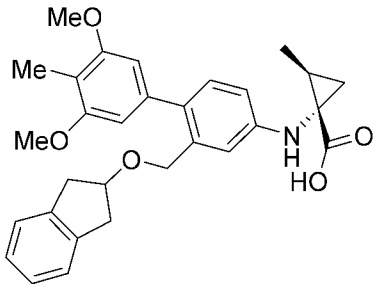
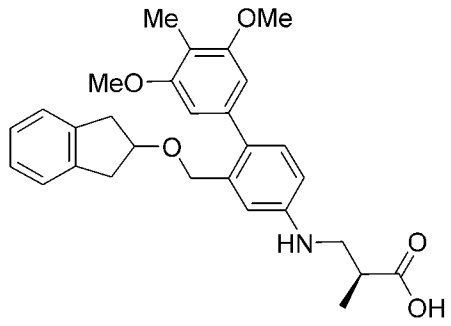
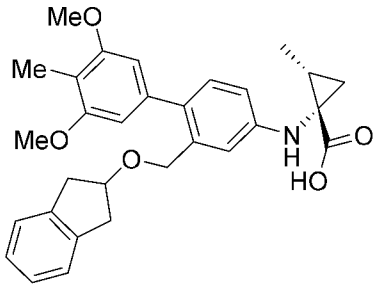
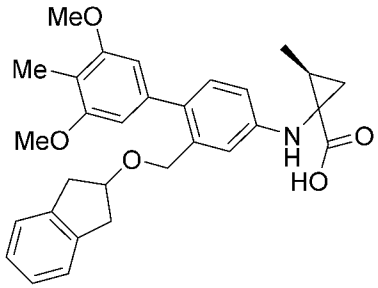
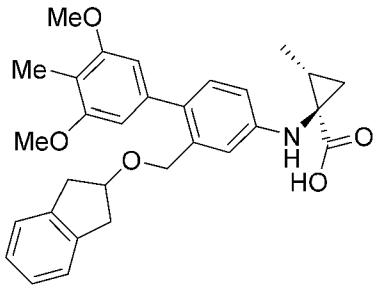
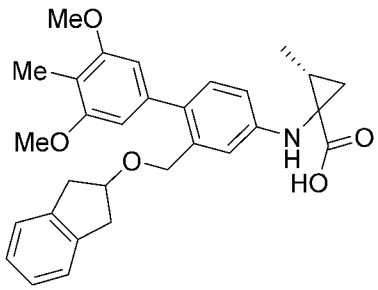
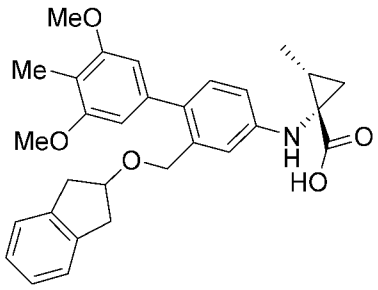
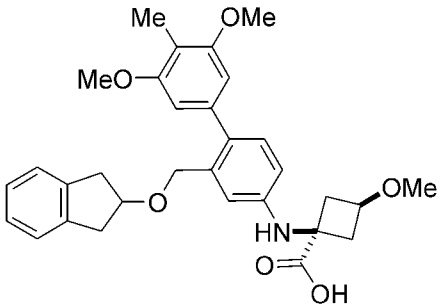
409	
410	
411	
412	

Compound	Structure
413	
414	
415	
416	
417	

[0172] The compounds of Formula I provided herein encompass stereochemical forms of the compounds, for example, optical isomers, such as enantiomers, diastereomers, as well as mixtures thereof, e.g., mixtures of enantiomers and/or diastereomers, including racemic mixtures, as well as equal or non-equal mixtures of individual enantiomers and/or diastereomers. All stereochemical forms are contemplated in this disclosure. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. Representative stereochemical forms are provided throughout the specification, including but not limited to those delineated in Table 2. In some embodiments, provided is compound selected from Table 2, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof:

Table 2

Structure	Structure
	
	
	
	
	

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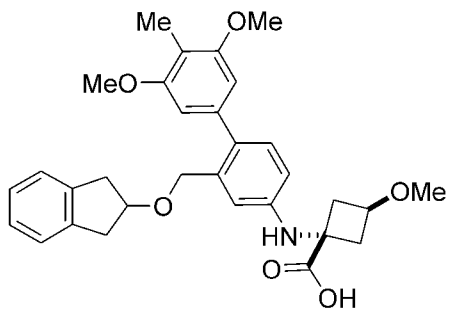
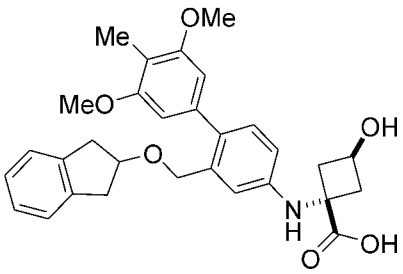
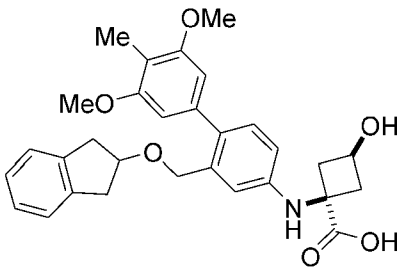
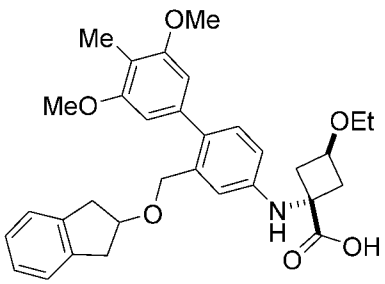
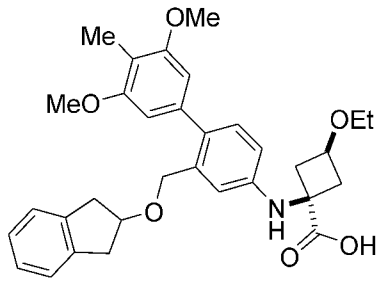

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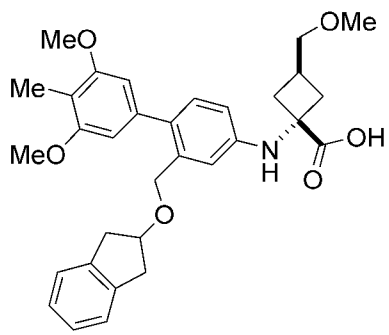
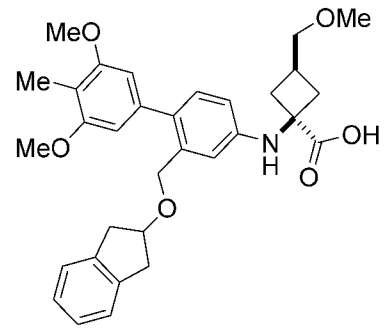
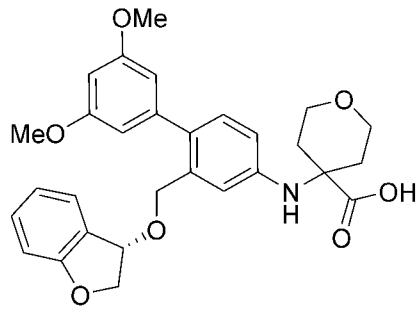
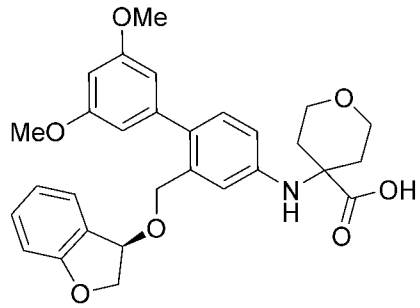

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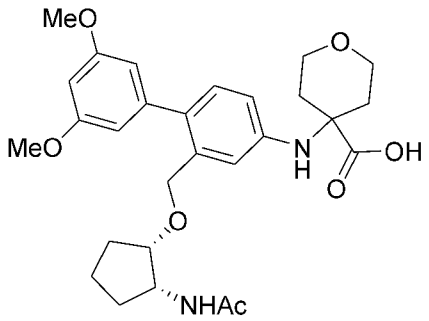
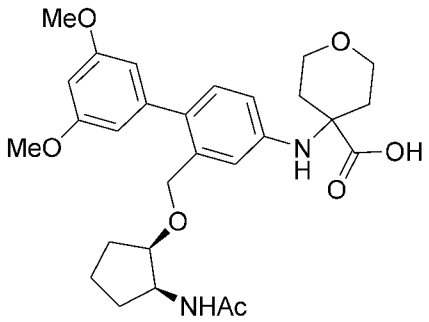
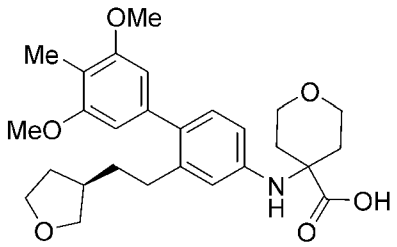
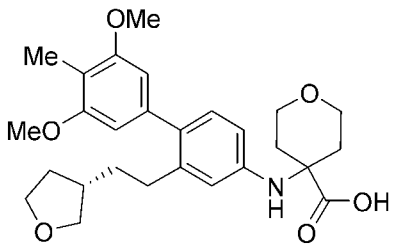
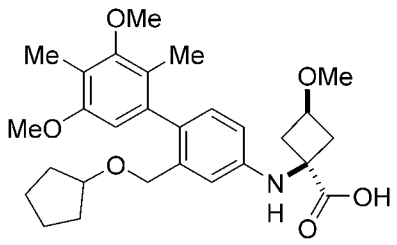

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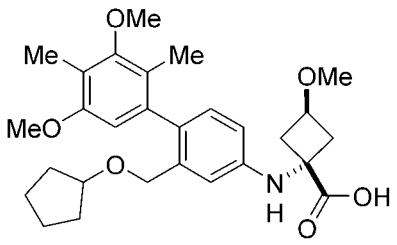
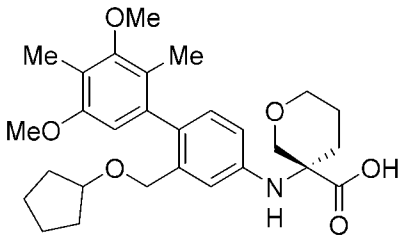
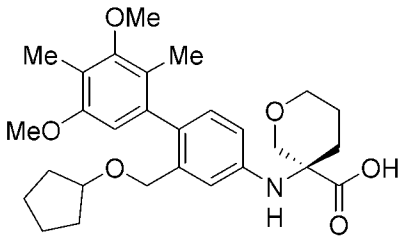
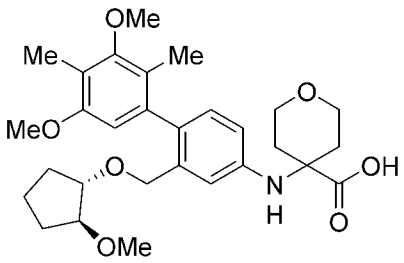
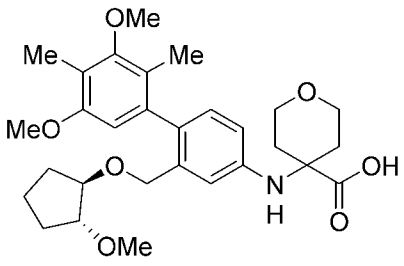

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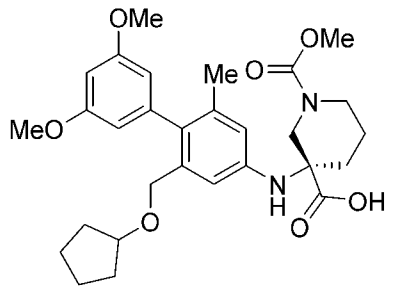
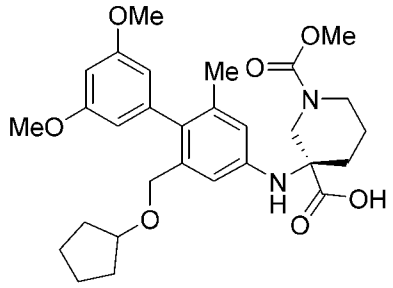
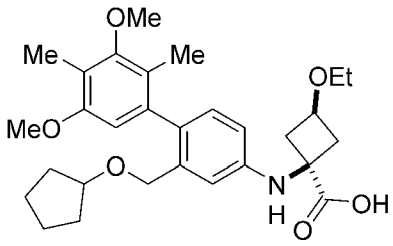
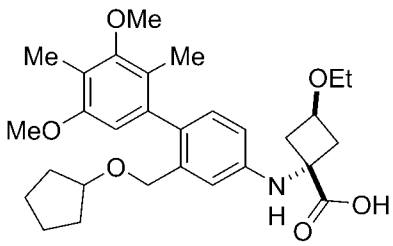
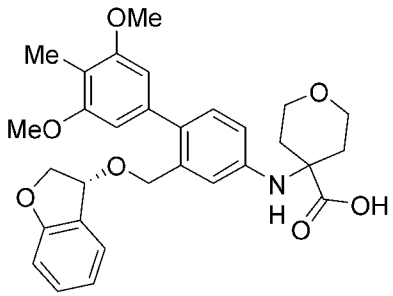

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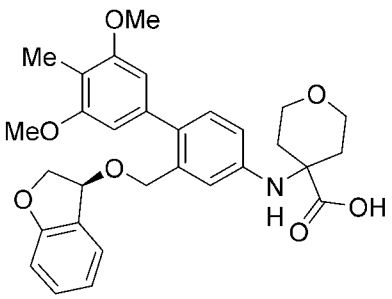
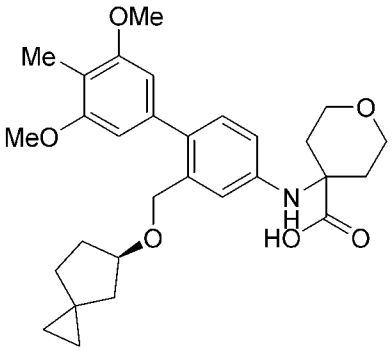
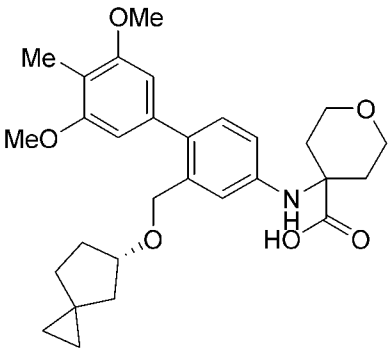
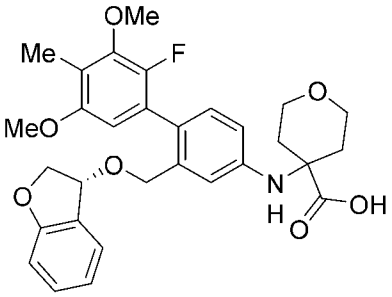

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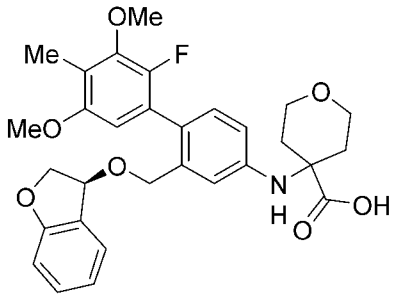
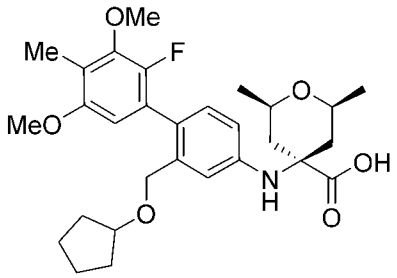
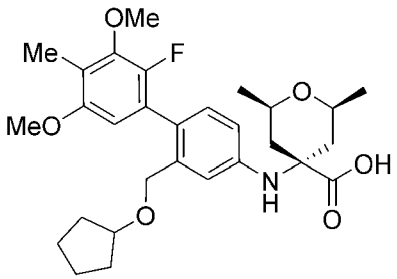
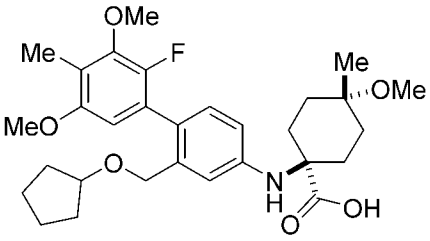
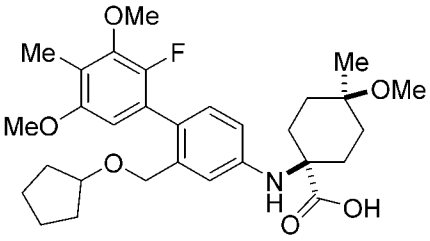

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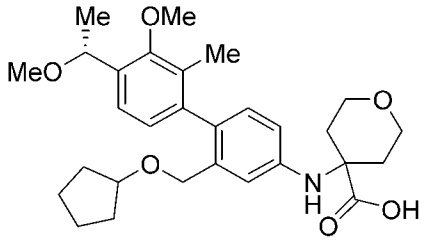
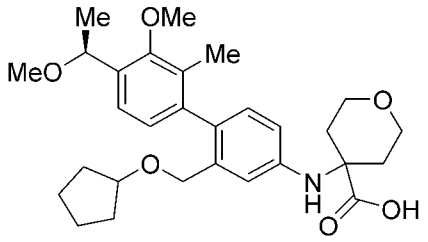
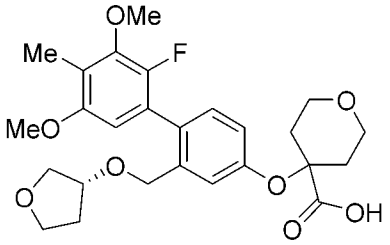
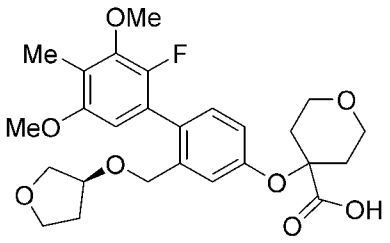
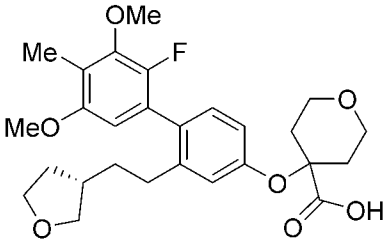
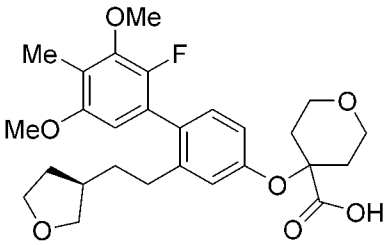

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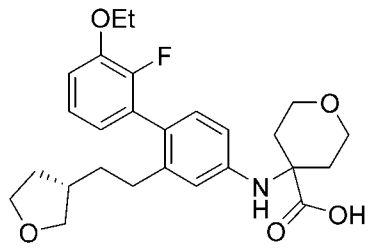
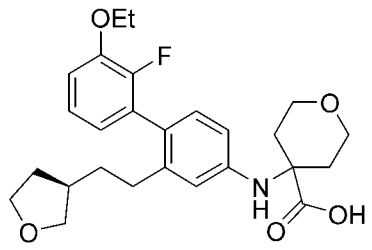
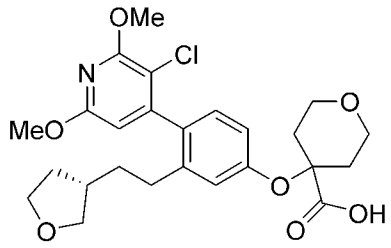
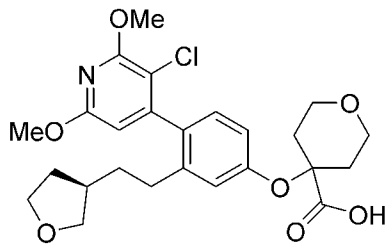
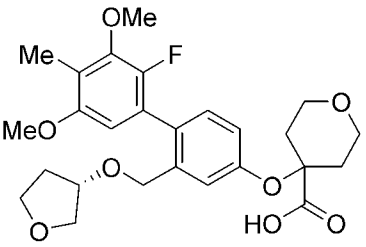
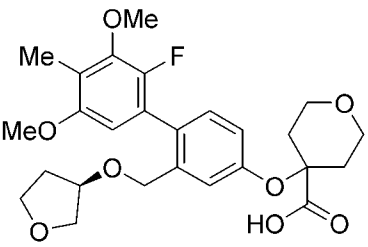

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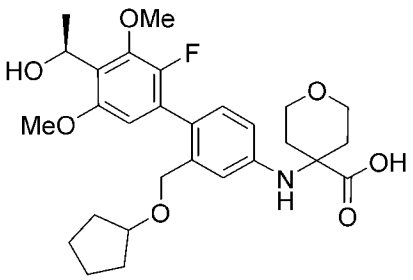
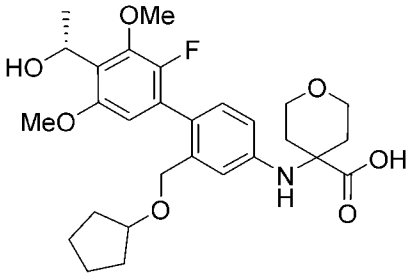
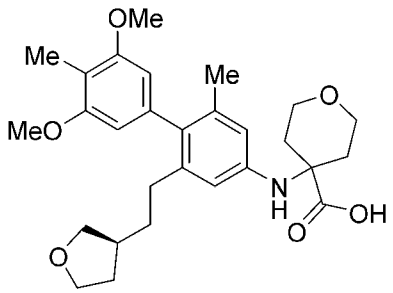
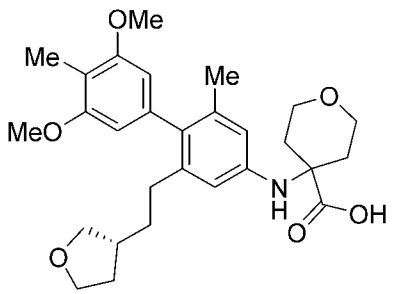





[0173] The compounds of Formula I include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula I also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula I and/or for separating enantiomers of compounds of Formula I. Non-limiting examples of pharmaceutically acceptable salts of compounds of Formula I include trifluoroacetic acid salts.

[0174] It will further be appreciated that the compounds of Formula I or their salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope of the present disclosure. For example, compounds of Formula I and salts thereof can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like.

Treatment Methods and Uses

[0175] The methods described herein may be applied to cell populations *in vivo* or *ex vivo*. "*In vivo*" means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. "*Ex vivo*" means outside of a living individual. Examples of *ex vivo* cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. In this context, the compounds and compositions described herein may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds and compositions described herein may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a compound of the present disclosure for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the compounds and compositions described herein may be suited are described below or will become apparent to those skilled in the art. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[0176] The compounds as provided herein, or pharmaceutically acceptable salts or solvates thereof, or pharmaceutical compositions of such compounds, are useful as inhibitors of one or more LPA receptors. As described further herein, a compound antagonizing to an LPA receptor can be useful for prevention and/or treatment of diseases such as various kinds of disease including, for example, fibrosis (e.g., renal fibrosis, pulmonary fibrosis, hepatic fibrosis, arterial fibrosis, systemic sclerosis), urinary system disease, carcinoma-associated disease, proliferative disease, inflammation/immune system disease, disease by secretory dysfunction, brain-related disease, and chronic disease.

[0177] In some embodiments, this disclosure provides methods for treating a subject (e.g., a human) having a disease, disorder, or condition in which inhibition of one or more LPA receptors (i.e., an LPA-associated disease) is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. In some embodiments, the methods provided herein can include or further include treating one or more conditions associated, co-morbid or sequela with any one or more of the conditions provided herein.

[0178] Provided herein is a method for treating a LPA-associated disease, the method comprising administering to a subject in need thereof an effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as disclosed herein.

[0179] In some embodiments, an LPA-associated disease includes, but is not limited to treating fibrosis of an organ (e.g., liver, kidney, lung, heart, and skin), liver disease (acute hepatitis, chronic hepatitis, liver fibrosis, liver cirrhosis, portal hypertension, regenerative failure, non-alcoholic steatohepatitis (NASH), liver hypofunction, hepatic blood flow disorder, and the like), cell proliferative disease (e.g., cancer, including solid tumors, solid tumor metastasis, vascular fibroma, myeloma, multiple myeloma, Kaposi's sarcoma, leukemia, and chronic lymphocytic leukemia (CLL), and invasive metastasis of cancer cells, inflammatory disease (e.g., psoriasis, nephropathy, and pneumonia), gastrointestinal tract disease (e.g., irritable bowel syndrome (TBS), inflammatory bowel disease (IBD), and abnormal pancreatic secretion), renal disease, urinary tract-associated disease (e.g., benign prostatic hyperplasia or symptoms associated with neuropathic bladder disease, spinal cord tumor, hernia of intervertebral disk, spinal canal stenosis, symptoms derived from diabetes, lower urinary tract disease (e.g., obstruction of lower urinary tract), inflammatory disease of the lower urinary tract, dysuna, and frequent urination), pancreas disease, abnormal angiogenesis-associated disease (e.g., arterial obstruction), scleroderma, brain-associated disease (e.g., cerebral infarction and cerebral hemorrhage), neuropathic pain, peripheral neuropathy, ocular disease (e.g., age-related macular degeneration (AMD), diabetic retinopathy, proliferative vitreoretinopathy (PVR), cicatricial pemphigoid, and glaucoma filtration surgery scarring).

[0180] In some embodiments, provided herein are methods of treating or preventing fibrosis, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as disclosed herein. For example, the methods can include treating renal fibrosis, pulmonary fibrosis, hepatic fibrosis, arterial fibrosis or systemic sclerosis. In some embodiments,

provided herein are methods of treating pulmonary fibrosis (e.g., Idiopathic Pulmonary Fibrosis (IPF)), the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein.

[0181] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat or prevent fibrosis in a subject. For example, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, can be used to treat fibrosis of an organ or tissue in a subject. In some embodiments, provided herein is a method for preventing a fibrosis condition in a subject, the method comprising administering to the subject at risk of developing one or more fibrosis conditions a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein. For example, the subject may have been exposed to one or more environmental conditions that are known to increase the risk of fibrosis of an organ or tissue. In some embodiments, the subject has been exposed to one or more environmental conditions that are known to increase the risk of lung, liver or kidney fibrosis. In some embodiments, the subject has a genetic predisposition of developing fibrosis of an organ or tissue. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is administered to a subject to prevent or minimize scarring following injury. For example, the injury can include surgery.

[0182] Exemplary diseases, disorders, or conditions that involve fibrosis include, but are not limited to: lung diseases associated with fibrosis, for example, idiopathic pulmonary fibrosis, iatrogenic drug induced, occupational/environmental induced fibrosis (Farmer lung), granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease (scleroderma and others), alveolar proteinosis, langerhans cell granulonmatosis, lymphangioleiomyomatosis, inherited diseases (e.g., Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, and familial interstitial lung disease), pulmonary fibrosis secondary to systemic inflammatory disease such as rheumatoid arthritis, scleroderma, lupus, cryptogenic fibrosing alveolitis, radiation induced fibrosis,

chronic obstructive pulmonary disease (COPD), scleroderma, bleomycin induced pulmonary fibrosis, chronic asthma, silicosis, asbestos induced pulmonary or pleural fibrosis, acute lung injury, acute respiratory distress syndrome (ARDS), and acute respiratory distress (including bacterial pneumonia induced, trauma induced, viral pneumonia induced, ventilator induced, non-pulmonary sepsis induced, and aspiration induced). Chronic nephropathies associated with injury/fibrosis, kidney fibrosis (renal fibrosis), glomerulonephritis secondary to systemic inflammatory diseases such as lupus and scleroderma, tubulointerstitium fibrosis, glomerular nephritis, glomerular sclerosis, focal segmental, diabetes, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, allograft and Alport Syndrome; dermatological disorders, gut fibrosis, for example, scleroderma, and radiation induced gut fibrosis; liver fibrosis, for example, cirrhosis, alcohol induced liver fibrosis, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), toxic/drug induced liver fibrosis (e.g., hemochromatosis), biliary duct injury, primary biliary cirrhosis, infection or viral induced liver fibrosis (e.g., chronic HCV infection), inflammatory/immune disorders, and autoimmune hepatitis; head and neck fibrosis, for example, corneal scarring, e.g., LASIK (laser-assisted in situ keratomileusis), corneal transplant, and trabeculectomy; hypertrophic scarring, Duputren disease, cutaneous fibrosis, cutaneous sceroderma, keloids, e.g., burn induced or surgical; and other fibrotic diseases, e.g., sarcoidosis, scleroderma, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, chronic lymphocytic leukemia, tumor metastasis, transplant organ rejection (e.g., Bronchiolitis obliterans), endometriosis, neonatal respiratory distress syndrome, and neuropathic pain, fibromyalgia, mixed connective tissue disease, and Peyronie's disease.

[0183] Provided herein is a method of improving lung function in a subject comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, to the subject in need thereof. In some embodiments, the subject has been diagnosed as having lung fibrosis. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat idiopathic pulmonary fibrosis in a subject. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat usual interstitial pneumonia in a subject.

[0184] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is used to treat diffuse parenchymal interstitial lung diseases in subject such as iatrogenic drug induced, occupational/environmental induced fibrosis (Farmer lung), granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease (scleroderma and others), alveolar proteinosis, langerhans cell granulonmatosis, lymphangioleiomyomatosis, inherited diseases (e.g., Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, and familial interstitial lung disease).

[0185] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat post-transplant fibrosis associated with chronic rejection in a subject such as Bronchiolitis obliterans following a lung transplant.

[0186] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat cutaneous fibrosis in a subject such as cutaneous scleroderma, Dupuytren disease, and keloids.

[0187] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat hepatic fibrosis with or without cirrhosis in a subject. For example, toxic/drug induced (hemochromatosis), alcoholic liver disease, viral hepatitis (hepatitis B virus, hepatitis C virus, HCV), nonalcoholic liver disease (NAFLD, NASH), and metabolic and auto-immune disease.

[0188] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat renal fibrosis in a subject (e.g., tubulointerstitium fibrosis and glomerular sclerosis).

[0189] Further examples of diseases, disorders, or conditions as provided herein include atherosclerosis, thrombosis, heart disease, vasculitis, formation of scar tissue, restenosis, phlebitis, COPD (chronic obstructive pulmonary disease), pulmonary hypertension, pulmonary fibrosis, pulmonary

inflammation, bowel adhesions, bladder fibrosis and cystitis, fibrosis of the nasal passages, sinusitis, inflammation mediated by neutrophils, and fibrosis mediated by fibroblasts.

[0190] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is administered to a subject with fibrosis of an organ or tissue or with a predisposition of developing fibrosis of an organ or tissue with one or more other agents that are used to treat fibrosis. In some embodiments, the one or more agents include corticosteroids, immunosuppressants, B-cell antagonists, and uteroglobin.

[0191] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat a dermatological disorder in a subject. Such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, psoriasis, scleroderma, psoriatic lesions, dermatitis, contact dermatitis, eczema, urticaria, rosacea, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, or urticaria. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is used to treat systemic sclerosis.

[0192] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is useful to treat or prevent inflammation in a subject. For example, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) can be used in the treatment or prevention of inflammatory/immune disorders in a subject.

[0193] Examples of inflammatory/immune disorders include psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, eczema, allogeneic or xenogeneic transplantation (organ, bone marrow, stem cells and other cells and tissues) graft rejection, graft-versus-host disease, lupus erythematosus, inflammatory disease, type I diabetes, pulmonary fibrosis, dermatomyositis, Sjogren's syndrome, thyroiditis (e.g., Hashimoto's and autoimmune thyroiditis), myasthenia gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis and atopic dermatitis.

[0194] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of pain in a subject. In some embodiments, the pain is acute pain or chronic pain. In some embodiments, the pain is neuropathic pain.

[0195] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of fibromyalgia. Fibromyalgia is believed to stem from the formation of fibrous scar tissue in contractile (voluntary) muscles. Fibrosis binds the tissue and inhibits blood flow, resulting in pain.

[0196] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of cancer. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of malignant and benign proliferative disease. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to prevent or reduce proliferation of tumor cells, invasion and metastasis of carcinomas, pleural mesothelioma (Yamada, Cancer Sci., 2008, 99(8), 1603-1610) or peritoneal mesothelioma, cancer pain, bone metastases (Boucharaba et al, J Clin. Invest., 2004, 114(12), 1714-1725; Boucharaba et al, Proc. Natl. Acad. Sci., 2006, 103(25) 9643-9648). Provided herein is a method of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein. In some embodiments, the methods provided herein further include administration of a second therapeutic agent, wherein the second therapeutic agent is an anti-cancer agent.

[0197] The term "cancer," as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ

(thyroid), prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias) at any stage of the disease with or without metastases.

[0198] Further non-limiting examples of cancers include, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T- Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, Ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenstrom macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sezary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.

[0199] In some embodiments, provided herein is a method of treating an allergic disorder in a subject, the method comprising administration of a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), is useful for the treatment of respiratory diseases, disorders, or conditions in a subject. For example, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) can treat asthma (e.g., chronic asthma) in a subject.

[0200] The term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, eustachian tubes, trachea, bronchi, lungs, related muscles (e.g., diaphragm and intercostals), and nerves. Non-limiting examples of respiratory diseases include asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

[0201] The term "asthma" as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate cause.

[0202] Further provided herein are methods for treating or preventing chronic obstructive pulmonary disease in a subject comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein. Examples of chronic obstructive pulmonary disease include, but are not limited to, chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation, and cystic fibrosis.

[0203] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is useful in the treatment or prevention of a nervous system disorder in a subject. The term "nervous system disorder," as used herein, refers to conditions that alter the structure or function of the brain, spinal cord or peripheral nervous system, including but not limited to Alzheimer's Disease, cerebral edema, cerebral ischemia, stroke, multiple sclerosis, neuropathies, Parkinson's Disease, those found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as degenerative disk disease and sciatica.

[0204] In some embodiments, provided herein is a method for treating or preventing a CNS disorder in a subject. Non-limiting examples of CNS disorders include multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke, cerebral ischemia, retinal ischemia, post-surgical cognitive dysfunction, migraine, peripheral neuropathy/neuropathic pain, spinal cord injury, cerebral edema and head injury.

[0205] Also provided herein are methods of treating or preventing cardiovascular disease in a subject. The term "cardiovascular disease," as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue. For example, provided herein are methods for treating or preventing vasoconstriction, atherosclerosis and its sequelae myocardial ischemia, myocardial infarction, aortic aneurysm, vasculitis and stroke comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof).

[0206] In some embodiments, provided herein are methods for reducing cardiac reperfusion injury following myocardial ischemia and/or endotoxic shock comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof).

[0207] Further provided herein are methods for reducing the constriction of blood vessels in a subject comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof). For example, methods for lowering or preventing an increase in blood pressure of a subject comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) are provided herein.

[0208] The ability of test compounds to act as inhibitors of an LGA receptor can be demonstrated by assays known in the art. The activity of the compounds and compositions provided herein as LGA receptor inhibitors can be assayed in vitro, in vivo, or in a cell line.

[0209] For example, Chinese hamster ovary cells overexpressing human LPA1 can be plated overnight (15,000 cells/well) in microplates in DMEM/F12 medium. Following overnight culture, cells are loaded with calcium indicator dye for 30 minutes at 37 °C. The cells are then equilibrated to room temperature for 30 minutes before the assay. Test compounds solubilized in DMSO are transferred to a multiwell non-binding surface plate and diluted with assay buffer (e.g., IX HBSS with calcium/magnesium, 20 mM HEPES, and 0.1% fatty acid free BSA) to a final concentration of 0.5% DMSO. Diluted compounds are added to the cells at final concentrations ranging from 0.08 nM to 5 mM and are then incubated for 20 min at room temperature at which time LPA is added at final concentrations of 10 nM to stimulate the cells. The compound IC_{50} value is defined as the concentration of test compound which inhibited 50% of the calcium flux induced by LPA alone. IC_{50} values can be determined by fitting data to a 4-parameter logistic equation.

[0210] In another example, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein is dosed orally p.o. 2 hours to CD-1 female mice prior to an LPA challenge. The mice are then dosed via tail vein (IV) with 0.15 mL of LPA in 0.1%BSA/PBS (2 pg/pL). Exactly 2 minutes following the LPA challenge, the mice are euthanized by decapitation and the trunk blood is collected. These samples are collectively centrifuged and individual 75 pL samples are frozen at -20°C until performance of a histamine assay. The plasma histamine analysis can be run by standard EIA (Enzyme Immunoassay) methods. Plasma samples are thawed and diluted 1 :30 in 0.1% BSA in PBS. An EIA protocol for histamine analysis as previously described can be used in this assay.

[0211] LPA has a role as a biological effector molecule, and has a diverse range of physiological actions that include effects on blood pressure, platelet activation, and smooth muscle contraction, and a

variety of cellular effects, which include cell growth, cell rounding, neurite retraction, and actin stress fiber formation and cell migration. These effects are predominantly receptor mediated.

[0212] Activation of the LPA receptors (LPA_1, LPA_2, LPA_3, LPA_4, LPA_5, LPA_6) with LPA mediates a range of downstream signaling cascades. Non-limiting examples include, mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC) inhibition/activation, phospholipase C (PLC) activation/Ca2+ mobilization, arachidonic acid release, Akt/PKB activation, and the activation of small GTPases, Rho, ROCK, Rae, and Ras. Additional pathways that are affected by LPA receptor activation include, for example, cyclic adenosine monophosphate (cAMP), cell division cycle 42/GTP-binding protein (Cdc42), proto-oncogene serine/threonine-protein kinase Raf (c-RAF), proto- oncogene tyrosine-protein kinase Src (c-src), extracellular signal-regulated kinase (ERK), focal adhesion kinase (FAK), guanine nucleotide exchange factor (GEF), glycogen synthase kinase 3b (GSK3b), c-jun amino-terminal kinase (JNK), MEK, myosin light chain II (MLC II), nuclear factor kB (NF-kB), N-methyl-D-aspartate (NMDA) receptor activation, phosphatidylinositol 3-kinase (PBK), protein kinase A (PKA), protein kinase C (PKC), ms-related C3 botulinum toxin substrate 1 (RAC1). Nearly all mammalian cells, tissues and organs co-express several LPA-receptor subtypes, which indicates that LPA receptors signal in a cooperative manner. LPA1, LPA2, and LPA3 share high amino acid sequence similarity.

[0213] LPA_1 (previously called VZG-l/EDG-2/mrecl.3) couples with three types of G proteins, $G_{i/o}$, G_q, and $G_{12/13}$. Through activation of these G proteins, LPA induces a range of cellular responses through LPA_1 including, for example, cell proliferation, serum-response element (SRE) activation, mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC) inhibition, phospholipase C (PLC) activation, Ca^{2+} mobilization, Akt activation, and Rho activation.

[0214] Expression of LPA_1 is observed in the testis, brain, heart, lung, small intestine, stomach, spleen, thymus, and skeletal muscle of in mice. Similarly, LPA_1 is expressed in human tissues such as the brain, heart, lung, placenta, colon, small intestine, prostate, testis, ovary, pancreas, spleen, kidney, skeletal muscle, and thymus.

[0215] LPA_2 (EDG-4) also couples with three types of G proteins, $G_{i/o}$, G_q, and $G_{12/13}$, to mediate LPA-induced cellular signaling. Expression of LPA_2 is observed in the testis, kidney, lung, thymus, spleen, and stomach of adult mice and in the human testis, pancreas, prostate, thymus, spleen, and peripheral blood leukocytes. Expression of LPA_2 is upregulated in various cancer cell lines, and several human LPA_2 transcriptional variants with mutations in the 3'-untranslated region have been observed.

[0216] LPA_3 can mediate pleiotropic LPA-induced signaling that includes PLC activation, Ca^{2+} mobilization, AC inhibition/activation, and MAPK activation. Overexpression of LPA_3 in neuroblastoma

cells leads to neurite elongation. Expression of LPA_3 is observed in adult mouse testis, kidney, lung, small intestine, heart, thymus, and brain. In humans, it is found in the heart, pancreas, prostate, testis, lung, ovary, and brain (frontal cortex, hippocampus, and amygdala).

[0217] LPA_4 ($p2y_9$/GPR23) is of divergent sequence compared to LPA_1, LPA_2, and LPA_3 with closer similarity to the platelet-activating factor (PAF) receptor. LPA_4 mediates LPA induced Ca^{2+} mobilization and cAMP accumulation, and functional coupling to the G protein Gs for AC activation, as well as coupling to other G proteins. The LPA_4 gene is expressed in the ovary, pancreas, thymus, kidney and skeletal muscle.

[0218] LPA_5 (GPR92) is a member of the purinocluster of GPCRs and is structurally most closely related to LPA_4. LPA_5 is expressed in human heart, placenta, spleen, brain, lung and gut. LPAs also shows very high expression in the CD8+ lymphocyte compartment of the gastrointestinal tract.

[0219] LPA_6 (p2y5) is a member of the purinocluster of GPCRs and is structurally most closely related to LPA_4. LPA_6 is an LPA receptor coupled to the Gl2/13-Rho signaling pathways and is expressed in the inner root sheaths of human hair follicles.

[0220] Improvements in any of the foregoing response criteria are specifically provided by the methods of the present disclosure.

Combination Therapies

[0221] The compounds as provided herein, or pharmaceutically acceptable salts or solvates thereof, or pharmaceutical compositions of such compounds, are useful as inhibitors of one or more LPA receptors. As described further herein, a compound antagonizing to an LPA receptor can be useful for prevention and/or treatment of diseases such as various kinds of disease including, for example, fibrosis (e.g., renal fibrosis, pulmonary fibrosis, hepatic fibrosis, arterial fibrosis, systemic sclerosis), urinary system disease, carcinoma-associated disease, proliferative disease, inflammation/immune system disease, disease by secretory dysfunction, brain-related disease, and chronic disease.

[0222] In some embodiments, this disclosure provides methods for treating a subject (e.g., a human) having a disease, disorder, or condition in which inhibition of one or more LPA receptors (i.e., an LPA-associated disease) is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. In some embodiments, the methods provided herein can include or further include treating one or more conditions associated, co-morbid or sequela with any one or more of the conditions provided herein.

[0223] Provided herein is a method for treating a LPA-associated disease, the method comprising administering to a subject in need thereof an effective amount of a compound disclosed herein (e.g., a

compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as disclosed herein.

[0224] In some embodiments, an LPA-associated disease includes, but is not limited to treating fibrosis of an organ (e.g., liver, kidney, lung, heart, and skin), liver disease (acute hepatitis, chronic hepatitis, liver fibrosis, liver cirrhosis, portal hypertension, regenerative failure, non-alcoholic steatohepatitis (NASH), liver hypofunction, hepatic blood flow disorder, and the like), cell proliferative disease (e.g., cancer, including solid tumors, solid tumor metastasis, vascular fibroma, myeloma, multiple myeloma, Kaposi's sarcoma, leukemia, and chronic lymphocytic leukemia (CLL), and invasive metastasis of cancer cells, inflammatory disease (e.g., psoriasis, nephropathy, and pneumonia), gastrointestinal tract disease (e.g., irritable bowel syndrome (TBS), inflammatory bowel disease (IBD), and abnormal pancreatic secretion), renal disease, urinary tract-associated disease (e.g., benign prostatic hyperplasia or symptoms associated with neuropathic bladder disease, spinal cord tumor, hernia of intervertebral disk, spinal canal stenosis, symptoms derived from diabetes, lower urinary tract disease (e.g., obstruction of lower urinary tract), inflammatory disease of the lower urinary tract, dysuna, and frequent urination), pancreas disease, abnormal angiogenesis-associated disease (e.g., arterial obstruction), scleroderma, brain-associated disease (e.g., cerebral infarction and cerebral hemorrhage), neuropathic pain, peripheral neuropathy, ocular disease (e.g., age-related macular degeneration (AMD), diabetic retinopathy, proliferative vitreoretinopathy (PVR), cicatricial pemphigoid, and glaucoma filtration surgery scarring).

[0225] In some embodiments, provided herein are methods of treating or preventing fibrosis, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as disclosed herein. For example, the methods can include treating renal fibrosis, pulmonary fibrosis, hepatic fibrosis, arterial fibrosis or systemic sclerosis. In some embodiments, provided herein are methods of treating pulmonary fibrosis (e.g., Idiopathic Pulmonary Fibrosis (IPF)), the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein.

[0226] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat or prevent

fibrosis in a subject. For example, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, can be used to treat fibrosis of an organ or tissue in a subject. In some embodiments, provided herein is a method for preventing a fibrosis condition in a subject, the method comprising administering to the subject at risk of developing one or more fibrosis conditions a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein. For example, the subject may have been exposed to one or more environmental conditions that are known to increase the risk of fibrosis of an organ or tissue. In some embodiments, the subject has been exposed to one or more environmental conditions that are known to increase the risk of lung, liver or kidney fibrosis. In some embodiments, the subject has a genetic predisposition of developing fibrosis of an organ or tissue. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is administered to a subject to prevent or minimize scarring following injury. For example, the injury can include surgery.

[0227] Exemplary diseases, disorders, or conditions that involve fibrosis include, but are not limited to: lung diseases associated with fibrosis, for example, idiopathic pulmonary fibrosis, iatrogenic drug induced, occupational/environmental induced fibrosis (Farmer lung), granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease (scleroderma and others), alveolar proteinosis, langerhans cell granulonmatosis, lymphangioleiomyomatosis, inherited diseases (e.g., Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, and familial interstitial lung disease), pulmonary fibrosis secondary to systemic inflammatory disease such as rheumatoid arthritis, scleroderma, lupus, cryptogenic fibrosing alveolitis, radiation induced fibrosis, chronic obstructive pulmonary disease (COPD), scleroderma, bleomycin induced pulmonary fibrosis, chronic asthma, silicosis, asbestos induced pulmonary or pleural fibrosis, acute lung injury, acute respiratory distress syndrome (ARDS), and acute respiratory distress (including bacterial pneumonia induced, trauma induced, viral pneumonia induced, ventilator induced, non-pulmonary sepsis induced, and aspiration induced). Chronic nephropathies associated with injury/fibrosis, kidney fibrosis (renal fibrosis), glomerulonephritis secondary to systemic inflammatory diseases such as lupus and scleroderma, tubulointerstitium fibrosis, glomerular nephritis, glomerular sclerosis, focal segmental, diabetes, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, allograft and Alport Syndrome; dermatological disorders, gut fibrosis, for example, scleroderma, and radiation induced

gut fibrosis; liver fibrosis, for example, cirrhosis, alcohol induced liver fibrosis, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), toxic/drug induced liver fibrosis (e.g., hemochromatosis), biliary duct injury, primary biliary cirrhosis, infection or viral induced liver fibrosis (e.g., chronic HCV infection), inflammatory/immune disorders, and autoimmune hepatitis; head and neck fibrosis, for example, corneal scarring, e.g., LASIK (laser-assisted in situ keratomileusis), corneal transplant, and trabeculectomy; hypertrophic scarring, Duputren disease, cutaneous fibrosis, cutaneous sceroderma, keloids, e.g., burn induced or surgical; and other fibrotic diseases, e.g., sarcoidosis, scleroderma, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, chronic lymphocytic leukemia, tumor metastasis, transplant organ rejection (e.g., Bronchiolitis obliterans), endometriosis, neonatal respiratory distress syndrome, and neuropathic pain, fibromyalgia, mixed connective tissue disease, and Peyronie's disease.

[0228] Provided herein is a method of improving lung function in a subject comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, to the subject in need thereof. In some embodiments, the subject has been diagnosed as having lung fibrosis. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat idiopathic pulmonary fibrosis in a subject. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat usual interstitial pneumonia in a subject.

[0229] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is used to treat diffuse parenchymal interstitial lung diseases in subject such as iatrogenic drug induced, occupational/environmental induced fibrosis (Farmer lung), granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease (scleroderma and others), alveolar proteinosis, langerhans cell granulonmatosis, lymphangioleiomyomatosis, inherited diseases (e.g., Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, and familial interstitial lung disease).

[0230] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat post-transplant fibrosis associated with chronic rejection in a subject such as Bronchiolitis obliterans following a lung transplant.

[0231] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat cutaneous fibrosis in a subject such as cutaneous scleroderma, Dupuytren disease, and keloids.

[0232] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat hepatic fibrosis with or without cirrhosis in a subject. For example, toxic/drug induced (hemochromatosis), alcoholic liver disease, viral hepatitis (hepatitis B virus, hepatitis C virus, HCV), nonalcoholic liver disease (NAFLD, NASH), and metabolic and auto-immune disease.

[0233] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat renal fibrosis in a subject (e.g., tubulointerstitium fibrosis and glomerular sclerosis).

[0234] Further examples of diseases, disorders, or conditions as provided herein include atherosclerosis, thrombosis, heart disease, vasculitis, formation of scar tissue, restenosis, phlebitis, COPD (chronic obstructive pulmonary disease), pulmonary hypertension, pulmonary fibrosis, pulmonary inflammation, bowel adhesions, bladder fibrosis and cystitis, fibrosis of the nasal passages, sinusitis, inflammation mediated by neutrophils, and fibrosis mediated by fibroblasts.

[0235] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat one or more symptoms of COVID-19.

[0236] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat chronic obstructive pulmonary disease (COPD).

[0237] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat neuroinflammation.

[0238] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat multiple sclerosis.

[0239] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is administered to a subject with fibrosis of an organ or tissue or with a predisposition of developing fibrosis of an organ or tissue with one or more other agents that are used to treat fibrosis. In some embodiments, the one or more agents include corticosteroids, immunosuppressants, B-cell antagonists, and uteroglobin.

[0240] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat a dermatological disorder in a subject. Such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, psoriasis, scleroderma, psoriatic lesions, dermatitis, contact dermatitis, eczema, urticaria, rosacea, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, or urticaria. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is used to treat systemic sclerosis.

[0241] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is useful to treat or prevent inflammation in a subject. For example, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) can be used in the treatment or prevention of inflammatory/immune disorders in a subject.

[0242] Examples of inflammatory/immune disorders include psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic

rhinitis, vaginitis, interstitial cystitis, scleroderma, eczema, allogeneic or xenogeneic transplantation (organ, bone marrow, stem cells and other cells and tissues) graft rejection, graft-versus-host disease, lupus erythematosus, inflammatory disease, type I diabetes, pulmonary fibrosis, dermatomyositis, Sjogren's syndrome, thyroiditis (e.g., Hashimoto's and autoimmune thyroiditis), myasthenia gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis and atopic dermatitis.

[0243] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of pain in a subject. In some embodiments, the pain is acute pain or chronic pain. In some embodiments, the pain is neuropathic pain.

[0244] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of fibromyalgia. Fibromyalgia is believed to stem from the formation of fibrous scar tissue in contractile (voluntary) muscles. Fibrosis binds the tissue and inhibits blood flow, resulting in pain.

[0245] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of cancer. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used in the treatment of malignant and benign proliferative disease. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a pharmaceutical composition as provided herein, is used to prevent or reduce proliferation of tumor cells, invasion and metastasis of carcinomas, pleural mesothelioma (Yamada, Cancer Sci., 2008, 99(8), 1603-1610) or peritoneal mesothelioma, cancer pain, bone metastases (Boucharaba et al, J Clin. Invest., 2004, 114(12), 1714-1725; Boucharaba et al, Proc. Natl. Acad. Sci., 2006, 103(25) 9643-9648). Provided herein is a method of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or a

pharmaceutical composition as provided herein. In some embodiments, the methods provided herein further include administration of a second therapeutic agent, wherein the second therapeutic agent is an anti-cancer agent.

[0246] The term "cancer," as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias) at any stage of the disease with or without metastases.

[0247] Further non-limiting examples of cancers include, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T- Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, Ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenstrom macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney)

cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sezary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.

[0248] In some embodiments, provided herein is a method of treating an allergic disorder in a subject, the method comprising administration of a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), is useful for the treatment of respiratory diseases, disorders or conditions in a subject. For example, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) can treat asthma (e.g., chronic asthma) in a subject.

[0249] The term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, eustachian tubes, trachea, bronchi, lungs, related muscles (e.g., diaphragm and intercostals), and nerves. Non-limiting examples of respiratory diseases include asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

[0250] The term "asthma" as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate cause.

[0251] Further provided herein are methods for treating or preventing chronic obstructive pulmonary disease in a subject comprising administering a therapeutically effective amount of a

compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein. Examples of chronic obstructive pulmonary disease include, but are not limited to, chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation, and cystic fibrosis.

[0252] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is useful in the treatment or prevention of a nervous system disorder in a subject. The term "nervous system disorder," as used herein, refers to conditions that alter the structure or function of the brain, spinal cord or peripheral nervous system, including but not limited to Alzheimer's Disease, cerebral edema, cerebral ischemia, stroke, multiple sclerosis, neuropathies, Parkinson's Disease, those found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as degenerative disk disease and sciatica.

[0253] In some embodiments, provided herein is a method for treating or preventing a CNS disorder in a subject. Non-limiting examples of CNS disorders include multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke, cerebral ischemia, retinal ischemia, post-surgical cognitive dysfunction, migraine, peripheral neuropathy/neuropathic pain, spinal cord injury, cerebral edema and head injury.

[0254] Also provided herein are methods of treating or preventing cardiovascular disease in a subject. The term "cardiovascular disease," as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue. For example, provided herein are methods for treating or preventing vasoconstriction, atherosclerosis and its sequelae myocardial ischemia, myocardial infarction, aortic aneurysm, vasculitis and stroke comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof).

[0255] In some embodiments, provided herein are methods for reducing cardiac reperfusion injury following myocardial ischemia and/or endotoxic shock comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof).

[0256] Further provided herein are methods for reducing the constriction of blood vessels in a subject comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof). For example, methods for lowering or preventing an increase in blood pressure of a subject comprising administering a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) are provided herein.

Pharmaceutical Compositions and Modes of Administration

[0257] Compounds provided herein are usually administered in the form of pharmaceutical compositions.

[0258] When employed as pharmaceuticals, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), including pharmaceutically acceptable salts or solvates thereof, can be administered in the form of a pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or can be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

[0259] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), in combination with one or more pharmaceutically acceptable excipients (carriers). For example, a pharmaceutical composition prepared using a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof). In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is a solid oral formulation. In some embodiments, the composition is formulated as a tablet or capsule.

[0260] Further provided herein are pharmaceutical compositions containing a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) with a pharmaceutically acceptable excipient. Pharmaceutical compositions containing a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as the active ingredient can be prepared by intimately mixing a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms

depending upon the desired route of administration (e.g., oral, parenteral). In some embodiments, the composition is a solid oral composition.

[0261] Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers can be found in The Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

[0262] Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1–3, edited by Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1–2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1–2, edited by Lieberman et al; published by Marcel Dekker, Inc.

[0263] Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α-, β, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds as provided herein. Dosage forms or compositions containing a chemical entity as provided herein in the range of 0.005% to 100% with the balance made up from non-toxic excipient may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington: The Science and Practice of Pharmacy, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

[0264] In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), or pharmaceutical compositions as provided herein can be administered to a subject in need thereof by any accepted route of

administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal (e.g., intranasal), nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal. In some embodiments, a preferred route of administration is parenteral (e.g., intratumoral).

[0265] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein or pharmaceutical compositions thereof can be formulated for parenteral administration, e.g., formulated for injection via the intraarterial, intrasternal, intracranial, intravenous, intramuscular, sub-cutaneous, or intraperitoneal routes. For example, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure. In some embodiments, devices are used for parenteral administration. For example, such devices may include needle injectors, microneedle injectors, needle-free injectors, and infusion techniques.

[0266] In some embodiments, the pharmaceutical forms suitable for injection include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In some embodiments, the form must be sterile and must be fluid to the extent that it may be easily injected. In some embodiments, the form should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[0267] In some embodiments, the carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. In some embodiments, the proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. In some embodiments, the prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for

example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In some embodiments, isotonic agents, for example, sugars or sodium chloride are included. In some embodiments, prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0268] In some embodiments, sterile injectable solutions are prepared by incorporating a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In some embodiments, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In some embodiments, sterile powders are used for the preparation of sterile injectable solutions. In some embodiments, the methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0269] In some embodiments, pharmacologically acceptable excipients usable in a rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol, Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methyloxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM) , lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

[0270] In some embodiments, suppositories can be prepared by mixing a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) or pharmaceutical compositions as provided herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In some embodiments, compositions for rectal administration are in the form of an enema.

[0271] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein or a pharmaceutical composition thereof is formulated for local delivery to the digestive or GI tract by way of oral administration (e.g., solid or liquid dosage forms.).

[0272] In some embodiments, solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. For example, in the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. In some embodiments, solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0273] In some embodiments, the pharmaceutical compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In some embodiments, another solid dosage form, a powder, marume, solution or suspension (e.g., in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). In some embodiments, unit dosage forms in which one or more compounds and pharmaceutical compositions as provided herein or additional active agents are physically separated are also contemplated; e.g., capsules with granules (or tablets in a capsule) of each

drug; two-layer tablets; two-compartment gel caps, etc. In some embodiments, enteric coated or delayed release oral dosage forms are also contemplated.

[0274] In some embodiments, other physiologically acceptable compounds may include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. For example, various preservatives are well known and include, for example, phenol and ascorbic acid.

[0275] In some embodiments, the excipients are sterile and generally free of undesirable matter. For example, these compositions can be sterilized by conventional, well-known sterilization techniques. In some embodiments, for various oral dosage form excipients such as tablets and capsules, sterility is not required. For example, the United States Pharmacopeia/National Formulary (USP/NF) standard can be sufficient.

[0276] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein or a pharmaceutical composition thereof is formulated for ocular administration. In some embodiments, ocular compositions can include, without limitation, one or more of viscogens (e.g., carboxymethylcellulose, glycerin, polyvinylpyrrolidone, polyethylene glycol); stabilizers (e.g., pluronic (triblock copolymers), cyclodextrins); preservatives (e.g., benzalkonium chloride, EDTA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

[0277] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein or a pharmaceutical composition thereof is formulated for topical administration to the skin or mucosa (e.g., dermally or transdermally). In some embodiments, topical compositions can include ointments and creams. In some embodiments, ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. In some embodiments, creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. For example, cream bases are typically water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. For example, the oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. In some embodiments, the emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. In some embodiments, as with other carriers or vehicles, an ointment base should be inert, stable, nonirritating, and non-sensitizing.

[0278] In any of the foregoing embodiments, pharmaceutical compositions as provided herein can include one or more one or more of lipids, interbilayer crosslinked multilamellar vesicles, biodegradable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

[0279] In some embodiments, the dosage for a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), is determined based on a multiple factors including, but not limited to, type, age, weight, sex, medical condition of the subject, severity of the medical condition of the subject, route of administration, and activity of the compound or pharmaceutically acceptable salt or solvate thereof. In some embodiments, proper dosage for a particular situation can be determined by one skilled in the medical arts. In some embodiments, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

[0280] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), is administered at a dose from about 0.01 to about 1000 mg. For example, from about 0.1 to about 30 mg, about 10 to about 80 mg, about 0.5 to about 15 mg, about 50 mg to about 200 mg, about 100 mg to about 300 mg, about 200 to about 400 mg, about 300 mg to about 500 mg, about 400 mg to about 600 mg, about 500 mg to about 800 mg, about 600 mg to about 900 mg, or about 700 mg to about 1000 mg. In some embodiments, the dose is a therapeutically effective amount.

[0281] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein is administered at a dosage of from about 0.0002 mg/Kg to about 100 mg/Kg (e.g., from about 0.0002 mg/Kg to about 50 mg/Kg; from about 0.0002 mg/Kg to about 25 mg/Kg; from about 0.0002 mg/Kg to about 10 mg/Kg; from about 0.0002 mg/Kg to about 5 mg/Kg; from about 0.0002 mg/Kg to about 1 mg/Kg; from about 0.0002 mg/Kg to about 0.5 mg/Kg; from about 0.0002 mg/Kg to about 0.1 mg/Kg; from about 0.001 mg/Kg to about 50 mg/Kg; from about 0.001 mg/Kg to about 25 mg/Kg; from about 0.001 mg/Kg to about 10 mg/Kg; from about 0.001 mg/Kg to about 5 mg/Kg; from about 0.001 mg/Kg to about 1 mg/Kg; from about 0.001 mg/Kg to about 0.5 mg/Kg; from about 0.001 mg/Kg to about 0.1 mg/Kg; from about 0.01 mg/Kg to about 50 mg/Kg; from about 0.01 mg/Kg to about 25 mg/Kg; from about 0.01 mg/Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 5 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from about 0.01 mg/Kg to about 0.5 mg/Kg; from about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0.1 mg/Kg to about 50 mg/Kg; from about 0.1 mg/Kg to about 25 mg/Kg; from about 0.1 mg/Kg to about 10 mg/Kg; from about 0.1 mg/Kg to about 5 mg/Kg;

from about 0.1 mg/Kg to about 1 mg/Kg; from about 0.1 mg/Kg to about 0.5 mg/Kg). In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein is administered as a dosage of about 100 mg/Kg.

[0282] In some embodiments, the foregoing dosages of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

[0283] In some embodiments, the period of administration of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) as provided herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In some embodiments, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 1 1 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is administered to a subject for a period of time followed by a separate period of time where administration of a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is stopped. In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) is

started and then a fourth period following the third period where administration is stopped. For example, the period of administration of a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof) followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In some embodiments, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In some embodiments, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

[0284] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), is orally administered to the subject one or more times per day (e.g., one time per day, two times per day, three times per day, four times per day per day or a single daily dose).

[0285] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), is administered by parenteral administration to the subject one or more times per day (e.g., 1 to 4 times one time per day, two times per day, three times per day, four times per day or a single daily dose).

[0286] In some embodiments, a compound disclosed herein (e.g., a compound of Formula I, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof), is administered by parenteral administration to the subject weekly.

Synthesis of the Compounds

[0287] The compounds of this disclosure can be prepared from readily available starting materials using, for example, the following general methods, and procedures. It will be appreciated that where certain process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

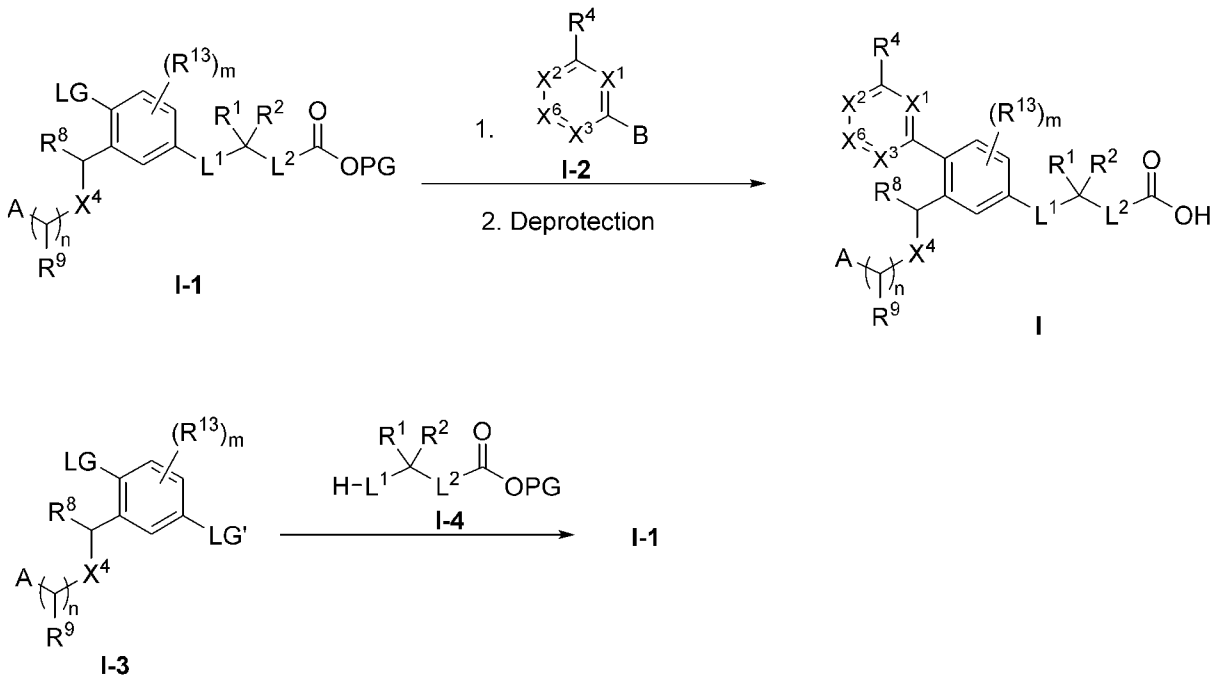
[0288] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting certain functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts (1999) Protecting Groups in Organic Synthesis, 3rd Edition, Wiley, New York, and references cited therein.

[0289] Furthermore, the compounds of this disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

[0290] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance CA USA), EMKA-Chemie Gmbh & Co. KG (Eching Germany), or Millipore Sigma (Burlington MA USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[0291] Scheme I illustrates a general method which can be employed for the synthesis of compounds described herein, where each wherein each of R^1, R^2, R^4, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, X^6, A, m, n, L^1 and L^2 are independently as defined herein, LG and LG' are a suitable leaving group, such as halo (e.g., Cl, Br, or I), where LG and LG' are not the same, PG is a suitable carboxyl protecting group, such as alkyl or benzyl, and B is a suitable coupling functional group such as, but not limited to, a boronic acid or a derivative thereof, such as a boronic ester (e.g., $-B(R^{50})_2$, where each R^{50} is independently an alkyl or substituted alkyl, or the two R^{50} join to form a cyclic boronic ester, which may be optionally substituted (e.g., pinacol boronic ester).

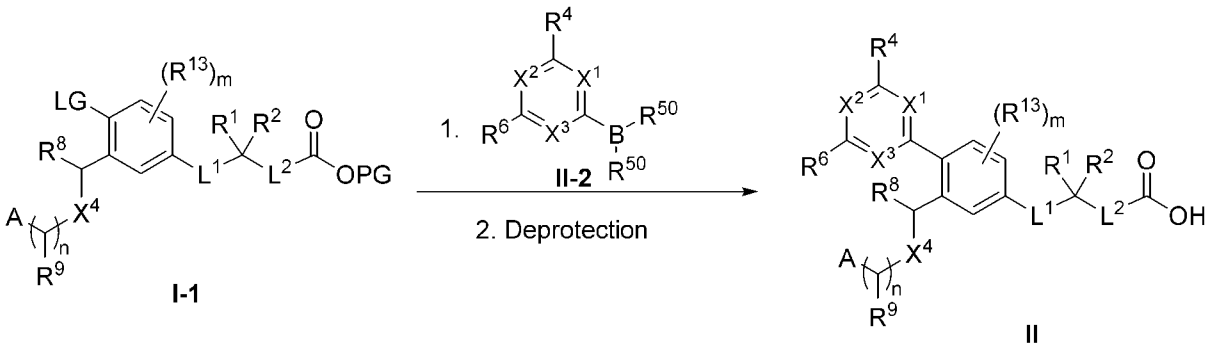
Scheme I



[0292] The compounds of Formula I are prepared by first coupling compound I-1, followed by deprotection to afford the free acid of Formula I, wherein B is a suitable coupling functional group such as, but not limited to, a boronic acid or a derivative thereof, such as a boronic ester (cyclic or acyclic), zinc or magnesium halide, an organotin compound, such as tributylstannane or trimethylstannane, fluorosulfonyl esters, tin, sodium, and the like. Such reactions are commonly utilized for aromatic functionalization, and are typically conducted in the presence of suitable catalyst such as, but not limited to, a palladium catalyst including [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or tris(dibenzylideneacetone)dipalladium(0), and the like, or a copper catalyst such as CuCl or CuI, and if required suitable mediator, co-catalyst and/or base known to one skilled in the art using suitable solvents/solvent mixtures. Upon reaction completion, compounds of Formula I can be recovered by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration and the like. In certain embodiments, when control of stereochemistry is desired, proper control of reaction conditions and selection of substituents for the reagents can at least partially dictate or preserve the formation of the various stereoisomers. Compounds I-1 and I-2 may be commercially obtained or synthesized *de novo*. For example, as shown above in Scheme I, Compound I-1 may be prepared by coupling compound I-3 with compound I-4 under standard nucleophilic aromatic substitution conditions.

[0293] Scheme II illustrates a general method which can be employed for the synthesis of compounds described herein, where each wherein each of R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, A, m, n, L^1 and L^2 are independently as defined herein, LG and LG' are a suitable leaving group, such as halo (e.g., Cl, Br, or I), where LG and LG' are not the same, PG is a suitable carboxyl protecting group, such as alkyl or benzyl, and B is a suitable coupling functional group such as, but not limited to, a boronic acid or a derivative thereof, such as a boronic ester (e.g., $-B(R^{50})_2$, where each R^{50} is independently an alkyl or substituted alkyl, or the two R^{50} join to form a cyclic boronic ester, which may be optionally substituted (e.g., pinacol boronic ester).

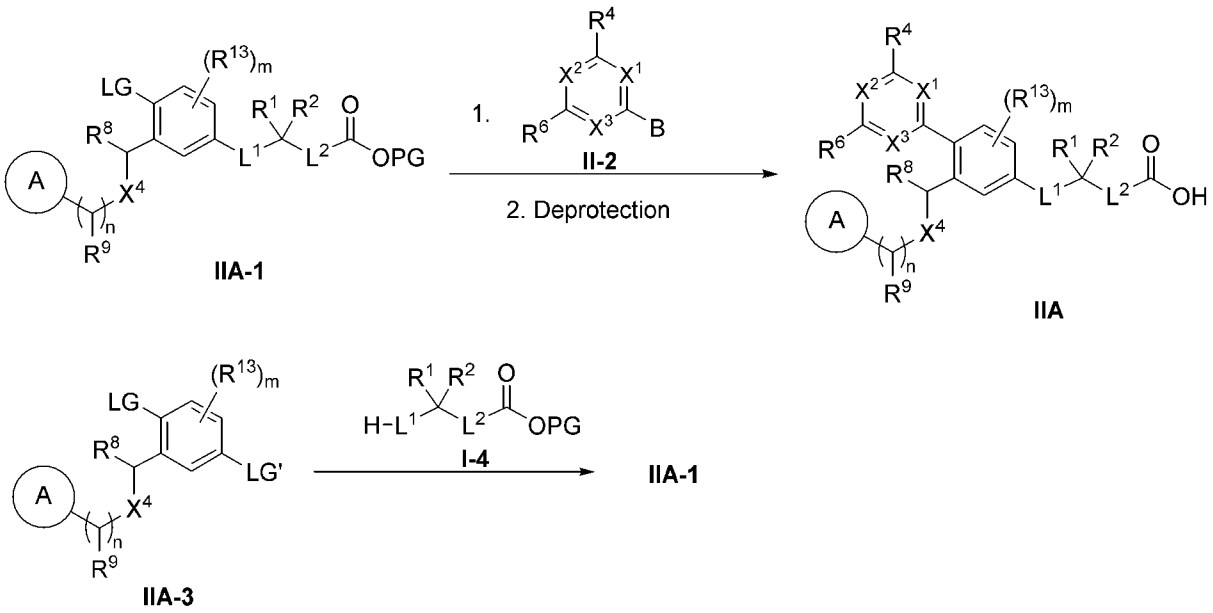
Scheme II



[0294] The compounds of Formula II are prepared by first coupling compound II-1, followed by deprotection to afford the free acid of Formula II, wherein B is a suitable functional group such as, but not limited to, a boronic acid or a derivative thereof, such as a boronic ester (cyclic or acyclic), zinc or magnesium halide, an organotin compound, such as tributylstannane or trimethylstannane, fluorosulfonyl esters, tin, sodium, hydrogen, and the like. Such reactions are commonly utilized for aromatic functionalization, and are typically conducted in the presence of suitable catalyst such as, but not limited to, a palladium catalyst including [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or tris(dibenzylideneacetone)dipalladium(0), and the like, or a copper catalyst such as CuCl or CuI, and if required suitable mediator, co-catalyst and/or base known to one skilled in the art using suitable solvents/solvent mixtures. Upon reaction completion, compounds of Formula II can be recovered by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration and the like. In certain embodiments, when control of stereochemistry is desired, proper control of reaction conditions and selection of substituents for the reagents can at least partially dictate or preserve the formation of the various stereoisomers. Compounds I-1 and II-2 may be commercially obtained or synthesized *de novo*.

[0295] Scheme III illustrates a general method which can be employed for the synthesis of compounds described herein, where each wherein each of R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, ring A, m, n, L^1 and L^2 are independently as defined herein, LG and LG' are a suitable leaving group, such as halo (e.g., Cl, Br, or I), where LG and LG' are not the same, PG is a suitable carboxyl protecting group, such as alkyl or benzyl, and B is a suitable coupling functional group such as, but not limited to, a boronic acid or a derivative thereof, such as a boronic ester (e.g., $-B(R^{50})_2$, where each R^{50} is independently an alkyl or substituted alkyl, or the two R^{50} join to form a cyclic boronic ester, which may be optionally substituted (e.g., pinacol boronic ester).

Scheme III



[0296] The compounds of Formula IIA are prepared by first coupling compound IIA-1, followed by deprotection to afford the free acid of Formula IIA, wherein B is a suitable functional group such as, but not limited to, a boronic acid or a derivative thereof, such as a boronic ester (cyclic or acyclic), zinc or magnesium halide, an organotin compound, such as tributylstannane or trimethylstannane, fluorosulfonyl esters, tin, sodium, hydrogen, and the like. Such reactions are commonly utilized for aromatic functionalization, and are typically conducted in the presence of suitable catalyst such as, but not limited to, a palladium catalyst including [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or tris(dibenzylideneacetone)dipalladium(0), and the like, or a copper catalyst such as CuCl or CuI, and if required suitable mediator, co-catalyst and/or base known to one skilled in the art using suitable solvents/solvent mixtures. Upon reaction completion, compounds of Formula IIA can be recovered by conventional techniques such as neutralization, extraction, precipitation,

chromatography, filtration and the like. In certain embodiments, when control of stereochemistry is desired, proper control of reaction conditions and selection of substituents for the reagents can at least partially dictate or preserve the formation of the various stereoisomers. Compounds IIA-1 and II-2 may be commercially obtained or synthesized *de novo*. For example, as shown above in Scheme III, Compound IIA-1 may be prepared by coupling compound IIA-3 with compound I-4 under standard nucleophilic aromatic substitution conditions.

[0297] It will be appreciated that the various substituents of each intermediate (e.g., compound I-1, II-1, I-2, I-3, II-3, and I-4) can be modified or added either before (as shown in Scheme I, Scheme II, or Scheme II) or after the addition of the I-2 or II-2 moiety. For example, A or the ring A may be appended before or after the steps shown in the Schemes above. The A or ring A moiety may be coupled to an X^4 precursor under substitution reaction conditions.

[0298] For any compound shown in Scheme I, Scheme II, or Scheme II, it should be understood that various derivatives can be provided by functional group interconversion at any step. In some embodiments, the various substituents of Formula I-1, II-1, IIA-1, I-2, II-2, I-3, II-3, IIA-3, or I-4, (e.g., A, ring A, R^1, R^2, R^4, R^6, R^8, R^9, R^{13}, X^1, X^2, X^3, X^4, X^6, m, n, L^1 and L^2) are as defined herein. However, derivatization of compounds I, II, IIA, I-1, II-1, IIA-1, I-2, II-2, I-3, II-3, IAI-3, or I-4, prior to reacting in any step, and/or further derivatization of the resulting reaction product, provides various compounds of Formula I, Formula II, or Formula IIA. Appropriate starting materials and reagents can be purchased or prepared by methods known to one of skill in the art. Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration, and the like. Other modifications to arrive at compounds of this disclosure are within the skill of the art.

General Synthesis

[0299] Typical embodiments of compounds described herein may be synthesized using the general reaction schemes described below. It will be apparent given the description herein that the general schemes may be altered by substitution of the starting materials with other materials having similar structures to result in products that are correspondingly different. Descriptions of syntheses follow to provide numerous examples of how the starting materials may vary to provide corresponding products. Given a desired product for which the substituent groups are defined, the necessary starting materials generally may be determined by inspection. Starting materials are typically obtained from commercial sources or synthesized using published methods. For synthesizing compounds which are embodiments described in the present disclosure, inspection of the structure of the compound to be synthesized will

provide the identity of each substituent group. The identity of the final product will generally render apparent the identity of the necessary starting materials by a simple process of inspection, given the examples herein. In general, compounds described herein are typically stable and isolatable at room temperature and pressure.

EXAMPLES

[0300] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

[0301] Abbreviations (as used herein):

AcOH	acetic acid
AgOTf	silver trifluoromethanesulfonate
AIBN	azobisisobutyronitrile
aq.	aqueous
Catacxium A-Pd-G2	Chloro[(di(1-adamantyl)-N-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (CAS: 1375477-29-4)
CCl_4	carbon tetrachloride
CH_3CN	acetonitrile
Cs_2CO_3	cesium carbonate
DCM or CH_2Cl_2	dichloromethane
CuI	copper(I) iodide
DAST	diethylaminosulfur trifluoride
DIBALH	diisobutylaluminium hydride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIAD	diisopropyl azodicarboxylate
DMAc or DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethyl-formamide

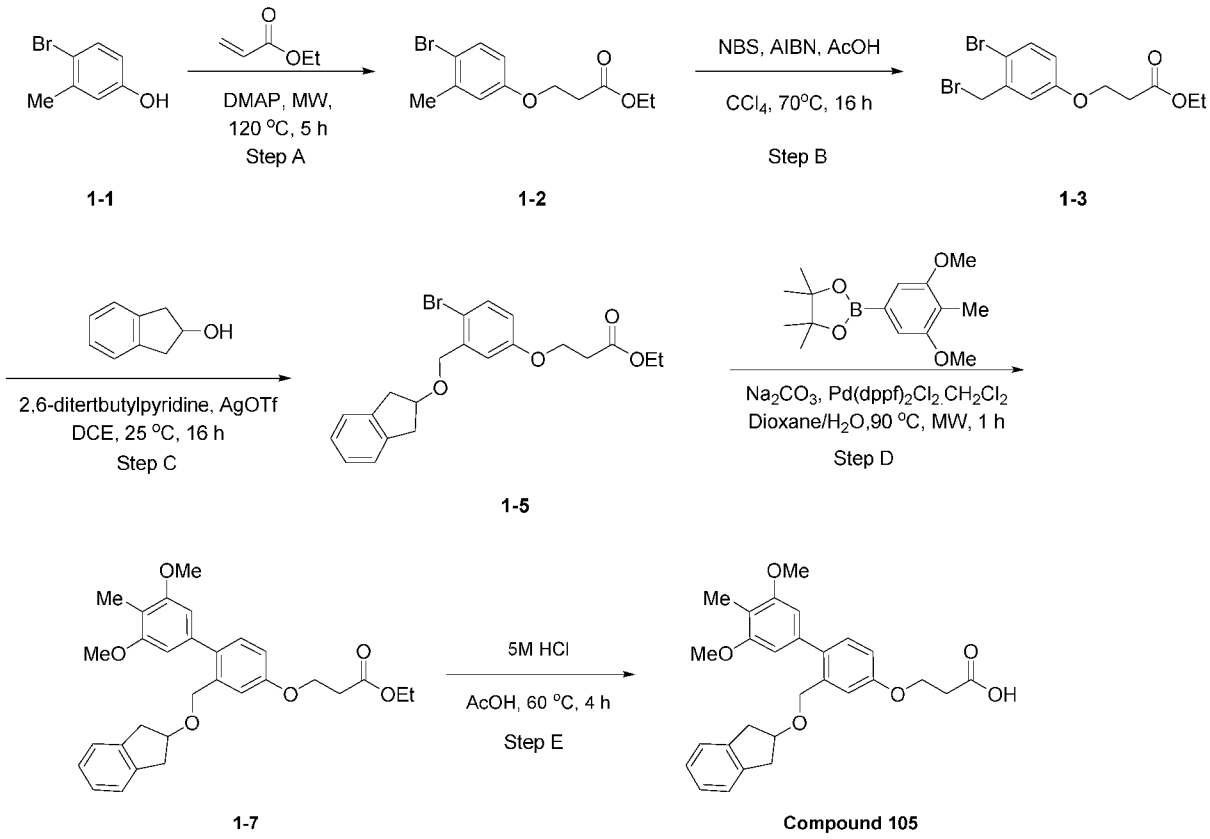
DPPA	diphenylphosphorazindate
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
h	hour
HCl	hydrochloric acid
H_2O	water
HPLC	High Performance Liquid Chromatography
prep. HPLC	Preparative High Performance Liquid Chromatography
$[Ir(COD)(OMe)]_2$	(1,5-cyclooctadiene)(methoxy)iridium(I) dimer
K_2CO_3	potassium carbonate
KOAc	potassium Acetate
LiCl	lithium chloride
LiOH	lithium hydroxide
MeI	iodomethane
MeOH	methanol
Na_2CO_3	sodium carbonate
Na_2SO_4	sodium sulfate
NaH	sodium hydride
NaI	sodium iodide
$NaNO_2$	sodium nitrite
NaOH	sodium hydroxide
NBS	bromosuccinimide
NH_4Cl	ammonium chloride
NFSI	N-fluorobenzenesulfonimide
NMP	1-methyl-pyrrolidin-2-one
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) chloride
$Pd(dppf)Cl_2.CH_2Cl_2$	[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) chloride-dichloromethane complex
$Pd(OAc)_2$	palladium (II) Acetate
PE	Petrol ether
PPh_3	triphenylphosphine
Prep. HPLC	Preparative High-Performance Liquid Chromatography

PTSA	*p*-toluenesulfonic acid
sat.	saturated
SFC	Supercritical Fluid Chromatography
S-Phos	2-Dicyclohexylphosphino-2',6'-diMethoxy-1,1'-biphenyl
t-BuOH	tert-butanol
t-BuOK	potassium tert-butoxide
t-BuONa	sodium tert-butoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
Xphos	dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane

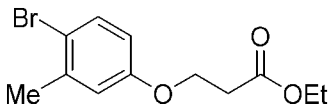
[0302] General information: All evaporations or concentrations were carried out in vacuo with a rotary evaporator. Analytical samples were dried *in vacuo* (1-5 mmHg) at rt. Thin layer chromatography (TLC) was performed on silica gel plates, spots were visualized by UV light (214 and 254 nm). Purification by column and flash chromatography was carried out using silica gel (100-200 mesh). Solvent systems were reported as mixtures by volume. NMR spectra were recorded on a Bruker 400 or Varian (400 MHz) spectrometer. ^{1}H chemical shifts are reported in δ values in ppm with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration. LCMS spectra were obtained on SHIMADZU LC20-MS2020 or Agilent 1260 series 6125B mass spectrometer or Agilent 1200 series, 6110 or 6120 mass spectrometer with electrospray ionization and excepted as otherwise indicated.

Example A1

3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)propanoic acid (Compound 105)

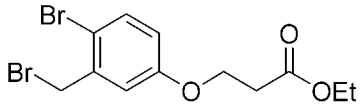


[0303] Step A: ethyl 3-(4-bromo-3-methylphenoxy)propanoate



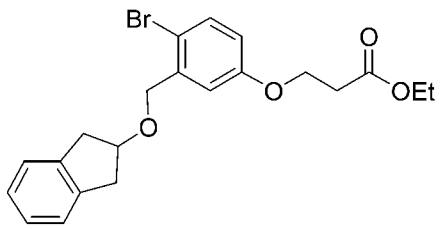
[0304] To a mixture of 4-bromo-3-methylphenol (3.20 g, 17.10 mmol) in ethyl acrylate (14 mL) was added DMAP (522 mg, 4.28 mmol) at room temperature. The mixture was stirred at 120 °C for 5 h under microwave irradiation. Then the reaction mixture was concentrated under reduced pressure. The residue was purified with silica gel column (PE/EtOAc = 20:1) to afford ethyl 3-(4-bromo-3-methylphenoxy)propanoate (1.20 g, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.62 (dd, J = 8.8 Hz, 3.2 Hz, 1H), 4.25 - 4.13 (m, 4H), 2.77 (t, J = 6.4 Hz, 2H), 2.35 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H).

[0305] Step B: ethyl 3-(4-bromo-3-(bromomethyl)phenoxy)propanoate



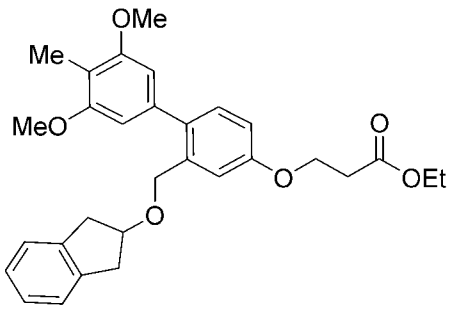
[0306] To a mixture of ethyl 3-(4-bromo-3-methylphenoxy)propanoate (300 mg, 1.04 mmol) in CCl_4 (8 mL) were added NBS (222 mg, 1.25 mmol), AIBN (7 mg, 0.042 mmol), and AcOH (0.15 mL). The reaction mixture was heated to 70 °C and stirred for 16 h. The reaction mixture was concentrated. The residue was diluted with water (10 mL), extracted with EtOAc (10 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified with *prep*. TLC (PE/EtOAc = 7/1) to afford ethyl 3-(4-bromo-3-(bromomethyl)phenoxy)propanoate (200 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 3.2 Hz, 1H), 6.74 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 4.54 (s, 2H), 4.28 - 4.13 (m, 4H), 2.78 (t, J = 6.4 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H).

[0307] Step C: ethyl 3-(4-bromo-3-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)phenoxy)propanoate



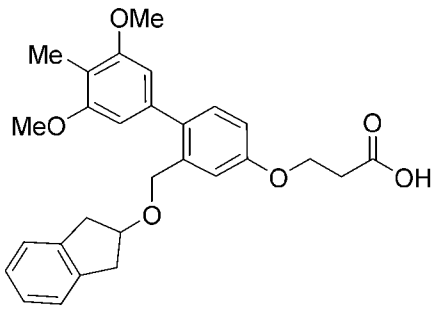
[0308] To a mixture of ethyl 3-(4-bromo-3-(bromomethyl)phenoxy)propanoate (220 mg, 0.60 mmol) and 2,3-dihydro-1H-inden-2-ol (139 mg, 1.05 mmol) in DCE (8 mL) were added 2,6-di-tert-butylpyridine (197 mg, 1.80 mmol) and AgOTf (269 mg, 1.05 mmol) at room temperature. The mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered and concentrated. The residue was purified with silica gel column (PE/EtOAc = 10:1) to afford ethyl 3-(4-bromo-3-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)phenoxy)propanoate (100 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 1H), 7.25 - 7.20 (m, 2H), 7.19 - 7.14 (m, 2H), 7.04 (d, J = 3.2 Hz, 1H), 6.70 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 4.59 (s, 2H), 4.54 - 4.47 (m, 1H), 4.28 - 4.12 (m, 4H), 3.23 (dd, J = 16.4 Hz, 6.4 Hz, 2H), 3.10 (dd, J = 16.0 Hz, 4.8 Hz, 2H), 2.76 (t, J = 6.4 Hz, 2H), 1.27 (t, J = 6.8 Hz, 3H).

[0309] Step D: ethyl 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)propanoate



[0310] To a mixture of ethyl 3-(4-bromo-3-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)phenoxy)propanoate (20.0 mg, 0.048 mmol) in 1,4-dioxane/H_2O (1 mL/ 0.2 mL) were added 2-(3,5-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20.0 mg, 0.072 mmol), Na_2CO_3 (15.2 mg, 0.144 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (2.00 mg, 0.0024 mmol) at room temperature. The reaction mixture was stirred at 90 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was filtered, and the filter cake was washed with EtOAc (10 mL). The filtrate was dried over Na_2SO_4 and concentrated. The residue was purified with *prep*. TLC (PE/EtOAc = 5/1) to afford ethyl 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-yl)oxy)propanoate (13.0 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 1H), 7.17 - 7.12 (m, 4H), 7.09 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.51 (s, 2H), 4.44 (s, 2H), 4.42 - 4.35 (m, 1H), 4.28 (t, J = 6.4 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.77 (s, 6H), 3.12 (dd, J = 16.0 Hz, 6.4 Hz, 2H), 2.97 (dd, J = 16.0 Hz, 4.4 Hz, 2H), 2.80 (t, J = 6.4 Hz, 2H), 2.14 (s, 3H), 1.29 (d, J = 7.2 Hz, 3H).

[0311] Step E: 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)propanoic acid (**Compound 105**)

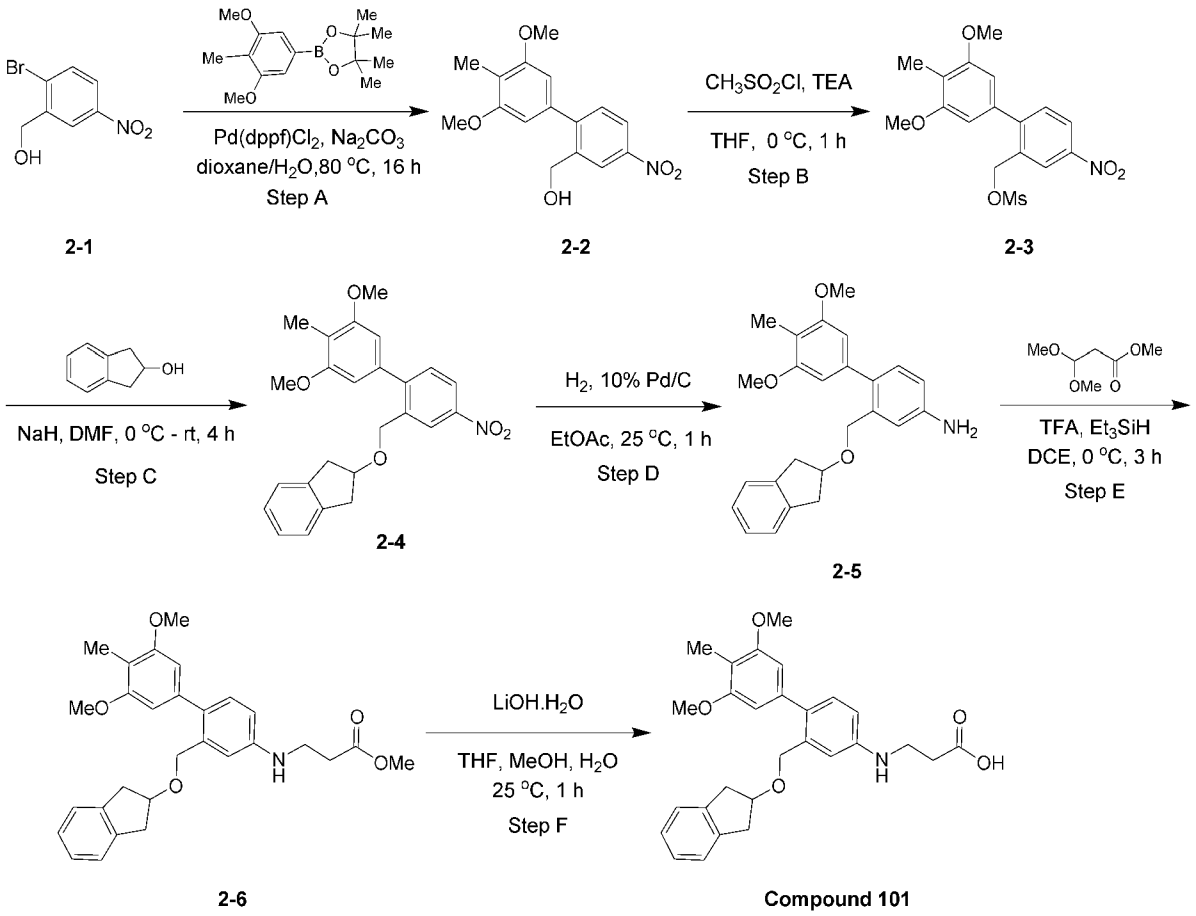


[0312] The mixture of ethyl 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-yl)oxy)propanoate (50.0 mg, 0.102 mmol) in AcOH (2 mL) and 5M *aq*. HCl solution (2 mL) was stirred at 60 °C for 4 h. The reaction mixture was concentrated. The residue was purified with *prep*. TLC (PE/EtOAc = 1/2) and further by *prep*. HPLC (0.1% formic acid in H_2O and

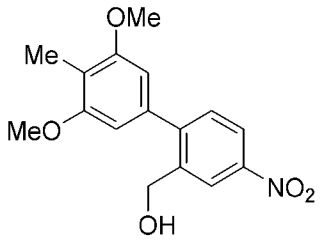
MeOH) to afford 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)propanoic acid (12.0 mg, 32% yield). LC-MS: m/z 485.3 $(M+Na)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 1H), 7.19 - 7.11 (m, 4H), 7.09 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.4 Hz, 2.8 Hz, 1H), 6.50 (s, 2H), 4.45 (s, 2H), 4.41 - 4.36 (m, 1H), 4.29 (t, J = 6.4 Hz, 2H), 3.77 (s, 6H), 3.12 (dd, J = 16.0 Hz, 6.4 Hz, 2H), 2.97 (dd, J = 16.4 Hz, 4.4 Hz, 2H), 2.87 (t, J = 6.0 Hz, 2H), 2.14 (s, 3H).

Example A2

3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)propanoic acid (Compound 101)

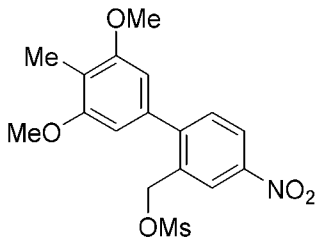


[0313] Step A: (3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl)methanol



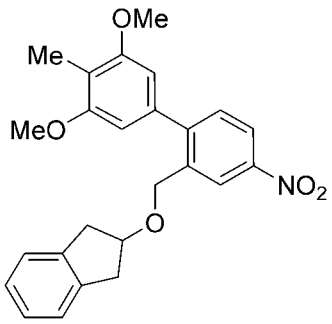
[0314] To a solution of (2-bromo-5-nitro-phenyl)methanol (2 g, 8.62 mmol) and 2-(3,5-dimethoxy-4-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.40 g, 8.62 mmol) in dioxane (30 mL) and H_2O (10 mL) was added Na_2CO_3 (2.74 g, 25.86 mmol) and $Pd(dppf)Cl_2$ (631 mg, 861.95 μmol). The mixture was stirred under nitrogen at 85 °C for 16 h. After cooling, the mixture was diluted with H_2O (15 mL), extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EtOAc = 10/1) to afford (3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl)methanol (2.2 g, 84% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.62 (s, 2H), 4.64 (s, 2H), 3.85 (s, 6H), 2.11 (s, 3H).

[0315] Step B: (3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl)methymethanesulfonate



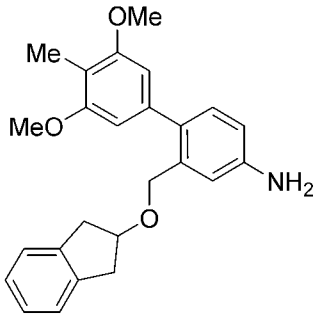
[0316] To a solution of [2-(3,5-dimethoxy-4-methyl-phenyl)-5-nitro-phenyl]methanol (2.2 g, 7.25 mmol) in THF (25 mL) was added TEA (1.47 g, 14.51 mmol) and MsCl (1.25 g, 10.88 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Then the mixture was diluted with H_2O (10 mL), extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EtOAc = 10/1) to afford (3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl) methylmethanesulfonate (2.50 g, 90% yield). ^1H NMR (400MHz, DMSO-d6) δ 8.49 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 6.67 (s, 2H), 5.32 (s, 2H), 3.83 (s, 6H), 3.24 (s, 3H), 2.06 (s, 3H).

[0317] Step C: 2-((3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl)methoxy)-2,3-dihydro-1H-indene



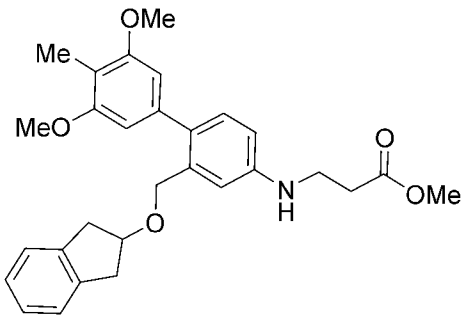
[0318] To a solution of indan-2-ol (1.42 g, 10.62 mmol) in THF (20 mL) was added NaH (424.71 mg, 10.62 mmol, 60% wt in mineral oil) at 0 °C. After being stirred for 30 min, to the above solution was added (3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl)methymethanesulfonate (2.7 g, 7.08 mmol) in THF (10 mL). The mixture was stirred at 25 °C for 12 h. The mixture was diluted with H_2O (30 mL), extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EtOAc = 10/1) to afford 2-((3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl)methoxy)-2,3-dihydro-1H-indene (220 mg, 7% yield). LC-MS: m/z 442.1 $(M+Na)^+$.

[0319] Step D: 4-(3,5-dimethoxy-4-methyl-phenyl)-3-(indan-2-yloxymethyl)aniline



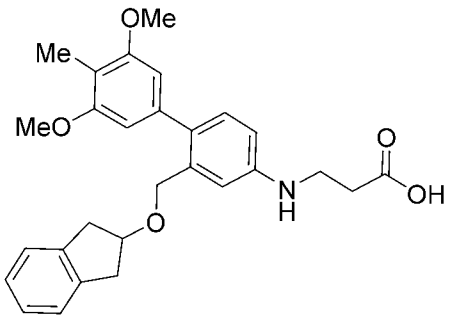
[0320] To a solution of 2-((3',5'-dimethoxy-4'-methyl-4-nitro-[1,1'-biphenyl]-2-yl)methoxy)-2,3-dihydro-1H-indene (200 mg, 47.68 μmol) in EtOAc (5 mL) was added 10% Pd/C (100 mg) under nitrogen. The suspension was degassed under vacuum and purged with H_2 for three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 1 h. The mixture was filtered and the filtrate was concentrated to afford 4-(3,5-dimethoxy-4-methyl-phenyl)-3-(indan-2-yloxymethyl)aniline (170 mg, 91% yield), which used for next step without purification. LC-MS: m/z 390.1 $(M+H)^+$.

[0321] Step E: methyl 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)propanoate



[0322] To a solution of 4-(3,5-dimethoxy-4-methyl-phenyl)-3-(indan-2-yloxymethyl)aniline (170 mg, 436.47 μmol) and methyl 3,3-dimethoxypropanoate (64.67 mg, 436.47 μmol) in DCE (5 mL) was added TFA (3.23 g, 28.37 mmol) and Et_3SiH (167 mg, 1.44 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EtOAc = 5/1) to afford methyl 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)propanoate (70 mg, 33% yield). LC-MS: m/z 476.2 $(M+H)^+$.

[0323] Step F: 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)propanoic acid (**Compound 101**)

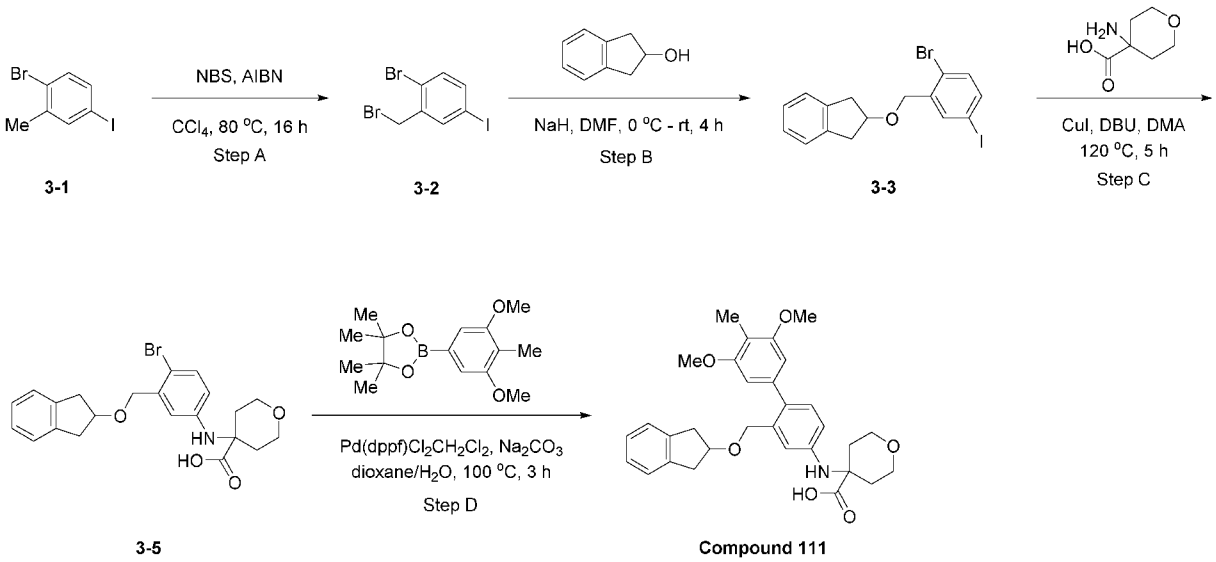


[0324] To a solution of methyl 3-[4-(3,5-dimethoxy-4-methyl-phenyl)-3-(indan-2-yloxymethyl)anilino]propanoate (50 mg, 105.14 μmol) in MeOH (1 mL), THF (1 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (22 mg, 525.68 μmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was acidified by 1N HCl to *p*H = 4, extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*. HPLC (Column: Phenomenex Gemini-NX 80* 30 mm* 3 um; mobile phase: [water (10 mM NH_4HCO_3) - CH_3CN]; B%: 12% - 82%, 9 min) to afford 3-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)propanoic acid (43 mg, 87% yield). LC-MS: m/z 462.0 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.18 - 7.06 (m, 5H), 6.81 (d, J =

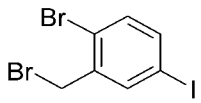
2.4 Hz, 1H), 6.67 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 6.54 (s, 2H), 4.43 (s, 2H), 4.41 - 4.36 (m, 1H), 3.73 (s, 6H), 3.43 (t, *J* = 6.8 Hz, 2H), 3.09 (dd, *J* = 16.0 Hz, 8.0 Hz, 2H), 2.89 (dd, *J* = 16.0 Hz, 4.0 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.09 (s, 3H).

Example A3

4-({2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]- 4-yl}amino)oxane-4-carboxylic acid (Compound 111)

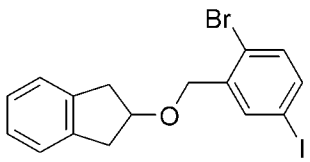


[0325] Step A: 1-bromo-2-(bromomethyl)-4-iodobenzene



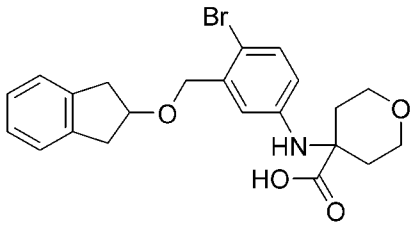
[0326] The mixture of bromo-4-iodo-2-methylbenzene (20.0 g, 67.36 mmol), AIBN (5.53 g, 33.68 mmol) and NBS (11.99 g, 67.36 mmol) in CCl_4 (300 mL) was heated to 80 °C and stirred for 16 h. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column (100% PE) to afford 1-bromo-2-(bromomethyl)-4-iodobenzene (8.0 g, 31.6% yield). Alternatively, 1-bromo-2-(bromomethyl)-4-iodobenzene is provided from (2-bromo-5-iodophenyl)methanol using PPh_3 and CBr_4 at 25 °C.

[0327] Step B: 2-[(2-bromo-5-iodophenyl)methoxy]-2,3-dihydro-1H-indene



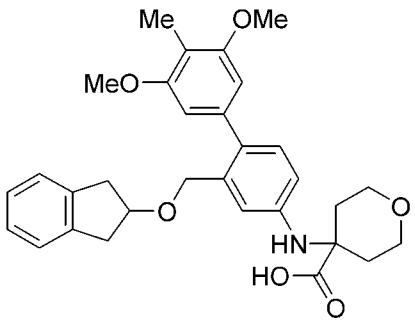
[0328] To the solution of 2,3-dihydro-1H-inden-2-ol (0.86 g, 6.39 mmol) in DMF (40 mL), was added NaH (319 mg, 7.98 mmol, 60% wt in mineral oil) under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Then a solution of 1-bromo-2-(bromomethyl)-4-iodobenzene (2.00 g, 5.32 mmol) in DMF (10 mL) was added into the above solution. The reaction mixture was stirred at room temperature for 3 h. Then the reaction mixture was quenched with *sat. aq.* NH_4Cl (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (0~10% EtOAc in PE) to afford 2-[(2-bromo-5-iodophenyl)methoxy]-2,3-dihydro-1H-indene (450 mg, 19.7% yield).

[0329] Step C: 4-({4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}amino)oxane- 4-carboxylic acid



[0330] To a solution of 2-[(2-bromo-5-iodophenyl)methoxy]-2,3-dihydro-1H-indene (450 mg, 1.05 mmol) in DMAc (10 mL) was added CuI (40 mg, 0.21 mmol), 4-aminotetrahydro-2*H*-pyran-4-carboxylic acid (304 mg, 2.10 mmol) and DBU (93.13 mg, 0.61 mmol). The resulting mixture was stirred at 120 °C for 5 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature, poured into water (20 mL). The *p*H value was adjusted to 7 by acetic acid. The resulting mixture was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (0-10% MeOH in CH_2Cl_2) to afford 4-({4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}amino)oxane-4-carboxylic acid (35 mg, 44.9% yield). LC-MS: m/z 447.9 $(M+H)^+$.

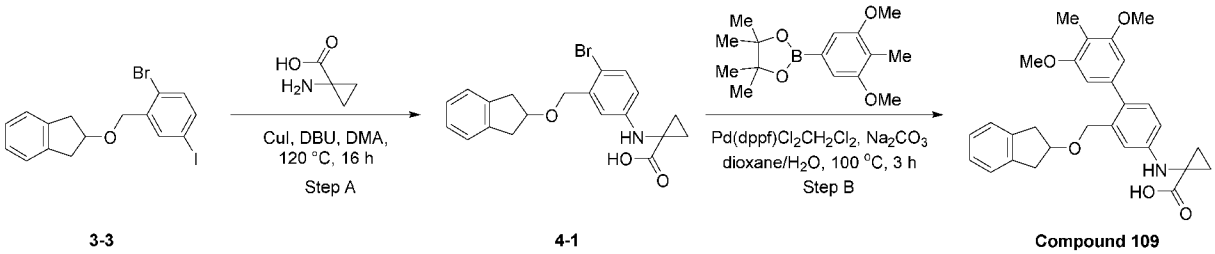
[0331] Step D: 4-({2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}amino)oxane-4-carboxylic acid (**Compound 111**)



[0332] The mixture of 4-({4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}amino)oxane-4-carboxylic acid (190 mg, 0.43 mmol), 2-(3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl- 1,3,2-dioxaborolane (118 mg, 0.43 mmol), Na_2CO_3 (135 mg, 1.28 mmol) and Pd(dppf)Cl_2. CH_2Cl_2 (69.35 mg, 0.09 mmol) in 1,4-dioxane (4 mL)/water (1 mL), was stirred at 100 °C for 3 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated. The residue was purified by *prep*. HPLC (Column: Xselect CSH C18 OBD Column 30*150 mm*5μm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: CH_3CN; Flow rate: 60 mL/min; Gradient: 30% B to 81% B in 10 min) to afford 4-({2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}-amino)oxane-4-carboxylic acid (102.8 mg, 45.9% yield). LC-MS: m/z 518.4 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 7.20 - 7.18 (m, 2H), 7.16 - 7.08 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 6.51 (s, 2H), 6.50 - 6.37 (m,1H) 4.36 - 4.33 (m, 3H), 3.72 (s, 6H), 3.71 - 3.59 (m, 4H), 3.10 (dd, J = 16.4 Hz, 6.3 Hz, 2H), 2.87 (dd, J = 16.4 Hz, 3.7 Hz, 2H), 2.08 - 1.97 (m, 2H), 1.91 - 1.89 (m, 2H).

Example A4

1-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)cyclopropane-1-carboxylic acid (Compound 109)

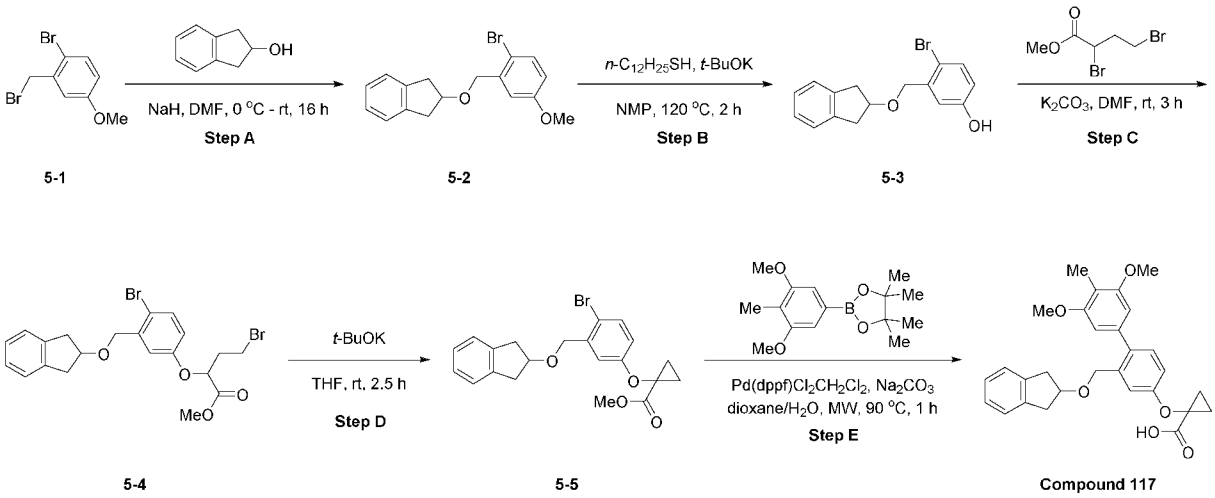


3-3 4-1 Compound 109

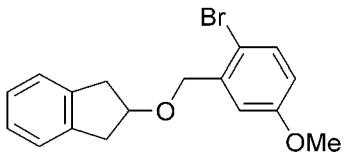
[0333] 1-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)cyclopropane-1-carboxylic acid **(Compound 109)** was synthesized according to the procedures described for the preparation of **Example A3** (step **C** and **D**) by using 1-aminocyclopropane-1-carboxylic acid in step **C**. LC-MS: m/z 496.2 $(M+Na)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 12.29 (brs, 1H), 7.21 - 7.16 (m, 2H), 7.15 - 7.09 (m, 2H), 7.04 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.58 - 6.56 (m, 2H), 6.54 (s, 2H), 4.38 - 4.30 (m, 3H), 3.73 (s, 6H), 3.08 (dd, J = 16.4 Hz, 6.0 Hz, 2H), 2.85 (dd, J = 16.4 Hz, 3.6 Hz, 2H), 2.01 (s, 3H), 1.47 - 1.39 (m, 2H), 1.03 - 0.96 (m, 2H).

Example A5

1-({2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}oxy)cyclopropane-1-carboxylic acid (Compound 117)

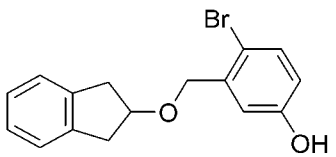


[0334] Step A: 2-[(2-bromo-5-methoxyphenyl)methoxy]-2,3-dihydro-1H-indene



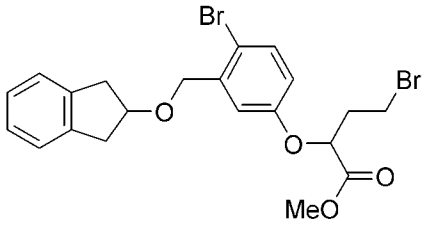
[0335] At 0 °C, to the solution of 2,3-dihydro-1H-inden-2-ol (3.59 g, 26.79 mmol) in DMF (50 mL) was added NaH (1.07 g, 26.79 mmol, 60% wt in mineral oil). The reaction mixture was stirred at 0 °C for 0.5 h. Then 1-bromo-2-(bromomethyl)-4-methoxybenzene (5.00 g, 17.86 mmol) was added to the above solution. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (50 mL x3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (0% to 10% EtOAc in PE) to afford 2-[(2-bromo-5-methoxyphenyl)methoxy]-2,3-dihydro-1H-indene (4.10 g, 68.9% yield).

[0336] Step B: 4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenol



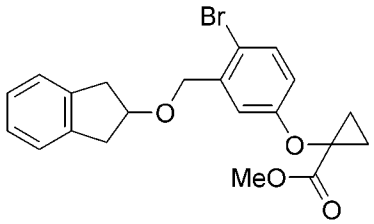
[0337] The mixture of dodecane-1-thiol (5.52 g, 32.41 mmol) and *t*-BuOK (3.64 g, 32.41 mmol) in NMP (100 mL) was stirred at room temperature for 10 min under nitrogen atmosphere. Then to the above mixture, was added 2-[(2-bromo-5-methoxyphenyl)methoxy]-2,3-dihydro-1H-indene (9.00 g, 27.01 mmol). The resulting mixture was stirred at 120 °C for 2 h under nitrogen atmosphere. After cooling, the reaction mixture was diluted with water (200 mL), neutralized to *p*H = 7 with *sat. aq.* NH_4Cl. The resulting mixture was extracted with EtOAc (100 mL x3). The combined organic layer was washed with brine (100 mL x3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by reverse flash column (30%-80% CH_3CN in water) to afford 4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenol (4.0 g, 11.6% yield). LC-MS: m/z 318.9 $(M-H)^-$.

[0338] Step C: methyl 4-bromo-2-{4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenoxy}-butanoate



[0339] The mixture of 4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenol (500 mg, 1.57 mmol), methyl 2,4-dibromobutanoate (489 mg, 1.88 mmol) and K_2CO_3 (432.98 mg, 3.13 mmol) in DMF (10 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (30 mL x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford crude methyl 4-bromo-2-{4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenoxy}butanoate (720 mg, 92.3% yield). LC-MS: m/z 520.8 $(M+Na)^+$.

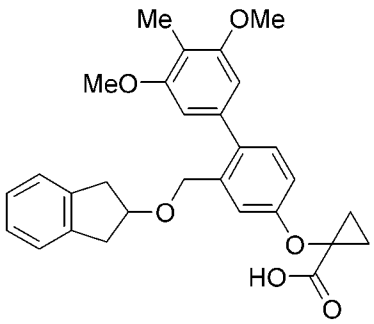
[0340] Step D: methyl 1-({4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}oxy)cyclopropane-1-carboxylate



[0341] The mixture of methyl 4-bromo-2-{4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenoxy}butanoate (710 mg, 1.43 mmol) and tert-butoxy potassium (320 mg, 2.85 mmol)

in THF (10 mL) was stirred at room temperature for 2.5 h. The reaction mixture was quenched with water (20 mL), extracted with EtOAc (30 mL x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated to afford crude methyl 1-({4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}oxy)cyclopropane-1-carboxylate (520 mg, 90.5% yield). LC-MS: m/z 440.9 $(M+Na)^+$.

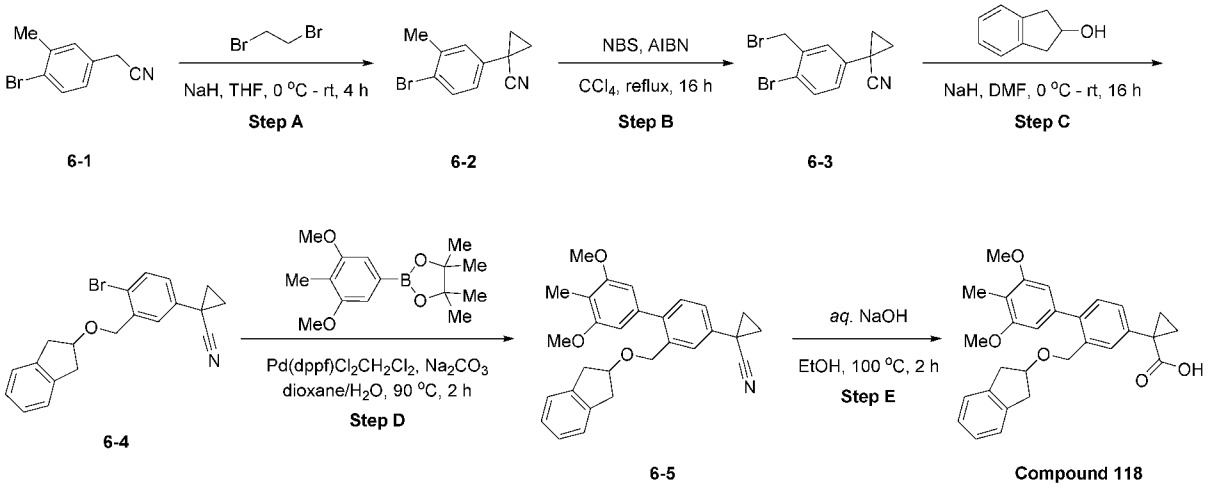
[0342] Step E: 1-({2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}oxy)cyclopropane-1-carboxylic acid **(Compound 117)**



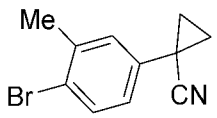
[0343] To the mixture of 1-{4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenoxy}cyclopropane-1-carboxylic acid (470 mg, 1.17 mmol), 2-(3,5-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (400 mg, 1.44 mmol) and Na_2CO_3 (370.58 mg, 3.50 mmol) in 1,4-dioxane (8 mL) and water (2 mL), was added $Pd(dppf)Cl_2.CH_2Cl_2$ (190 mg, 0.23 mmol). The reaction mixture was heated to 90 °C and stirred at 90 °C for 1 h under nitrogen under microware irradiation. After cooling, the reaction mixture was poured into water (100 mL), extracted with EtOAc (30 mL x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum. The residue was purified by *prep*. HPLC (Column: CHIRAL ART Cellulose-SB, 4.6*100 mm, 3μm; Mobile Phase A: Hex(0.1%FA): EtOH=90: 10; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5 mL) to afford 1-({2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}oxy)cyclopropane-1-carboxylic acid (8.3 mg, 1.5% yield). LC-MS: m/z 497.2 $(M+Na)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 7.21 - 7.07 (m, 5H), 6.97 (d, J = 2.6 Hz, 1H), 6.86 (dd, J = 8.4 Hz, 2.7 Hz, 1H), 6.56 (s, 2H), 4.38 (s, 2H), 4.37 - 4.36 (m, 1H), 3.73 (s, 6H), 3.10 - 3.00 (m, 2H), 2.90 - 2.80 (m, 2H), 2.02 (s, 3H), 1.42 - 1.30 (m, 2H), 1.00 - 0.90 (m, 2H).

Example A6

1-{2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}cyclopropane-1-carboxylic acid (Compound 118)

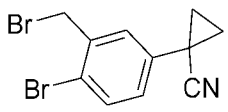


[0344] Step A: 1-(4-bromo-3-methylphenyl)cyclopropane-1-carbonitrile



[0345] To a solution of 2-(4-bromo-3-methylphenyl)acetonitrile (6.00 g, 28.56 mmol) in THF (120 mL), was added sodium hydride (1.14 g, 28.56 mmol, 60% wt in mineral oil) at 0 °C. After being stirred for 15 min, dibromoethane (5.37 g, 28.56 mmol) was added to the above reaction mixture. The resulting reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was quenched by ice water (200 mL), extracted with EtOAc (100 mL x3). The combined organic layer was washed with brine (200 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (10% to 20% EtOAc in PE) to afford 1-(4-bromo-3-methylphenyl)cyclopropane-1-carbonitrile (800 mg, 11.9% yield).

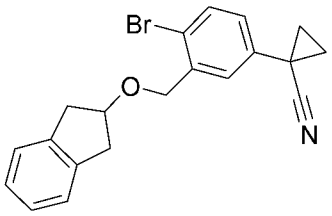
[0346] Step B: 1-[4-bromo-3-(bromomethyl)phenyl]cyclopropane-1-carbonitrile



[0347] To the mixture of 1-(4-bromo-3-methylphenyl)cyclopropane-1-carbonitrile (800 mg, 3.39 mmol) and NBS (1.21 g, 6.78 mmol) in CCl_4 (16 mL), was added AIBN (278 mg, 1.70 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at reflux for 16 h. After

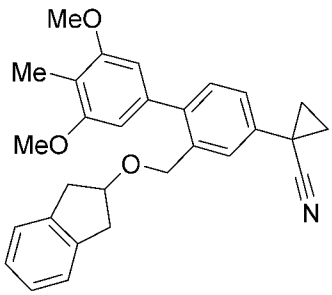
cooling, the reaction mixture was diluted with water (100 mL), extracted with CH_2Cl_2 (20 mL x3). The combined organic layer was washed with water (50 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (10%-20% EtOAc in PE) to afford 1-[4-bromo-3-(bromomethyl)phenyl]cyclopropane-1-carbonitrile (550 mg, 51.5% yield).

[0348] Step C: 1-{4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}cyclopropane-1-carbonitrile



[0349] To a solution of 1-[4-bromo-3-(bromomethyl)phenyl]cyclopropane-1-carbonitrile (500 mg, 1.59 mmol) in DMF (10 mL) was added sodium hydride (190 mg, 4.76 mmol, 60% wt in mineral oil) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. To the above reaction mixture, was added 2,3-dihydro-1H-inden-2-ol (639 mg, 4.76 mmol). The resulting reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched by ice water (20 mL), extracted with EtOAc (10 mL x3). The combined organic layer was washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (10%-20% EtOAc in PE) to afford 1-{4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}cyclopropane-1-carbonitrile (370 mg, 63.3% yield).

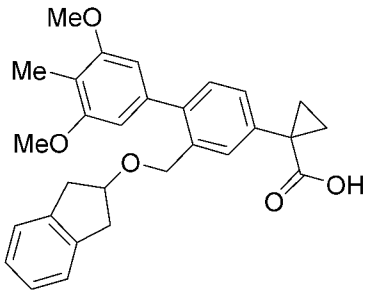
[0350] Step D: 1-{2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}cyclopropane-1-carbonitrile



[0351] To a stirred solution of 1-{4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}cyclopropane-1-carbonitrile (220 mg, 0.60 mmol), 2-(3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (199 mg, 0.716 mmol) and Na_2CO_3 (190 mg, 1.79 mmol) in 1,4-dioxane (4 mL) and water (0.8 mL), was added $Pd(dppf)Cl_2.CH_2Cl_2$ (49 mg, 0.06 mmol) at

room temperature under nitrogen atmosphere. The resulting mixture was stirred at 90 °C for 2 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column (10%-30% EtOAc in PE) to afford 1-{2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}cyclopropane-1-carbonitrile (220 mg, 83.8% yield). LC-MS: m/z 440.0 $(M+H)^+$.

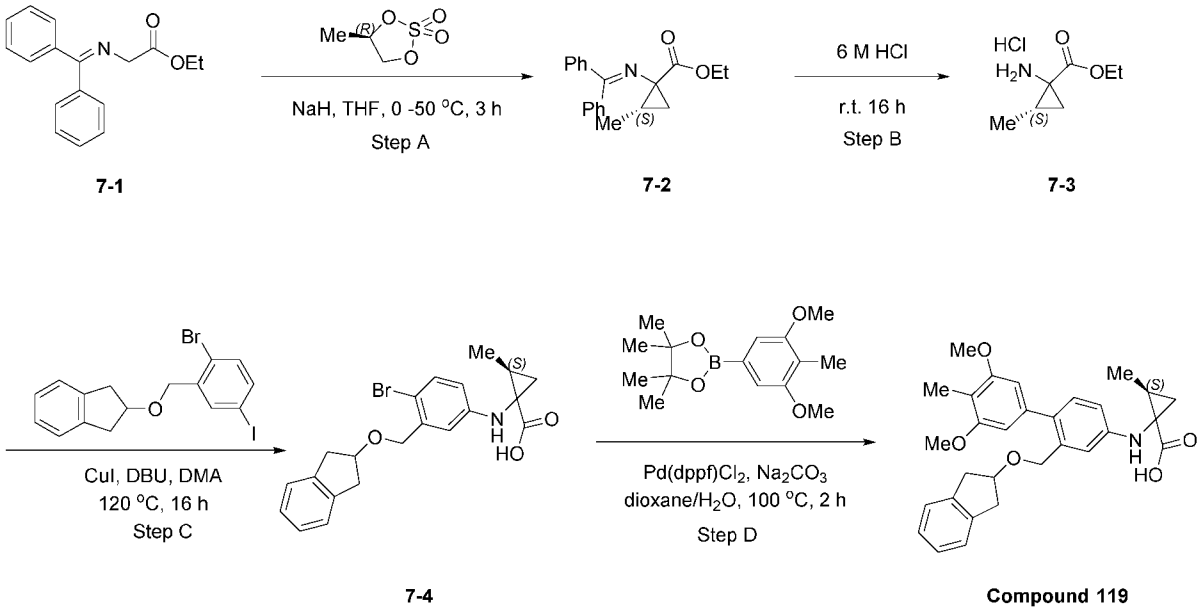
[0352] Step E: 1-{2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}cyclopropane-1-carboxylic acid **(Compound 118)**



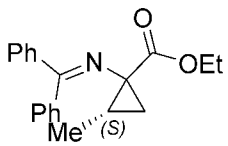
[0353] To a stirred solution of 1-{2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}cyclopropane-1-carbonitrile (100 mg, 0.29 mmol) in EtOH (5 mL) was added a solution of NaOH (500 mg, 12.5 mmol) in water (1 mL). The reaction mixture was stirred at 100 °C for 2 h under nitrogen atmosphere. After cooling, the reaction mixture was acidified to *p*H = 5 with 2 M HCl. The resulting mixture was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine (30 mL x3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*. HPLC (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.05%HCl), Mobile Phase B: CH_3CN; Flow rate: 60 mL/min; Gradient: 50% B to 90% B in 10 min) to afford 1-{2-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}cyclopropane-1-carboxylic acid (40.6 mg, 38.9% yield). LC-MS: m/z 457.0 $(M-H)^-$. ^1H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 7.41 (d, J = 1.9 Hz, 1H), 7.30 (dd, J = 7.8 Hz, 1.9 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.20 - 7.16 (m, 2H), 7.14 - 7.09 (m, 2H), 6.61 (s, 2H), 4.43 - 4.31 (m, 3H), 3.73 (s, 6H), 3.08 (dd, J = 16.4 Hz, 6.3 Hz, 2H), 2.86 (dd, J = 16.4 Hz, 3.7 Hz, 2H), 2.03 (s, 3H), 1.46 - 1.44 (m, 2H), 1.14 - 1.12 (m, 2H).

Example A7

(2S)-1-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl- [1,1'-biphenyl]-4-yl)amino)-2-methylcyclopropane-1-carboxylic acid (Compound 119)

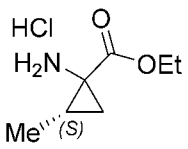


[0354] Step A: ethyl (2S)-1-((diphenylmethylene)amino)-2-methylcyclopropane-1-carboxylate

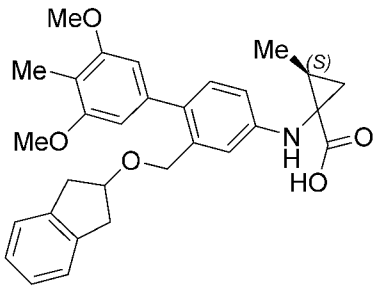


[0355] To a solution of ethyl 2-[(diphenylmethylidene)amino]acetate (5 g, 18.70 mmol) in THF (50 mL) was added NaH (1.35 g, 56.11 mmol, 60% wt in mineral oil) at 0 °C. After being stirred for 15 min, (R)-(-)-4-methyl-2,2-dioxo-1,3,2-dioxathiolane (2.28 g, 14.30 mmol) was added into the above solution. The resulting reaction mixture was heated to 50 °C and stirred for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was diluted with hexane (50 mL), filtered, the filter cake was washed with hexane (10 mL x3). The combined filtrate was concentrated under reduced pressure to afford ethyl (2S)-1-[(diphenylmethylidene)amino]-2-methylcyclopropane-1-carboxylate (3.4 g, crude). LC-MS: m/z 308.0 $(M+H)^+$.

[0356] Step B: ethyl (2S)-1-amino-2-methylcyclopropane-1-carboxylate hydrochloride



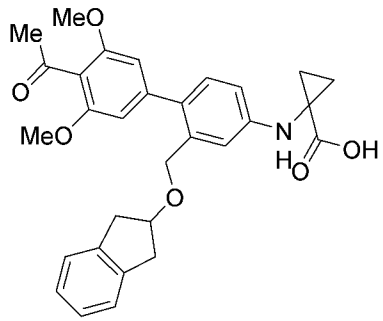
[0357] To the stirred solution of ethyl (2S)-1-[(diphenylmethylidene)amino]-2-methylcyclopropane-1-carboxylate (3.4 g, 11.06 mmol) in ether (35 mL) was added 6 M *aq*. HCl (3.87 mL, 13.27 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was extracted with EtOAc (20 mL x2). The combined water layer was concentrated under reduced pressure to afford ethyl (2S)-1-amino-2-methylcyclopropane-1-carboxylate hydrochloride (1.2 g, 60.4% yield).



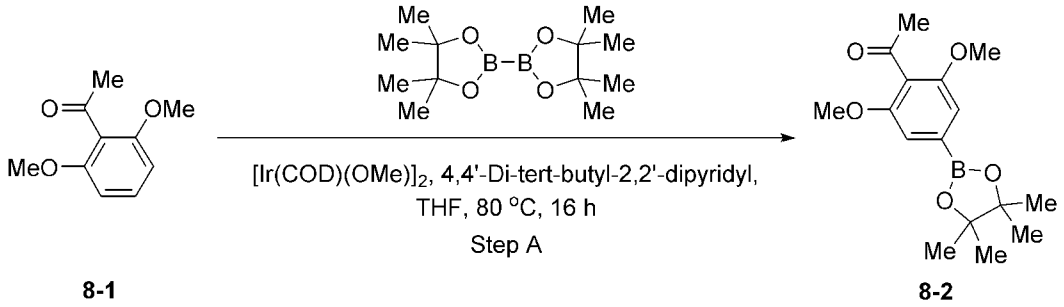
[0358] (2S)-1-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl- [1,1'-biphenyl]-4-yl)amino)-2-methylcyclopropane-1-carboxylic acid **(Compound 119)** was synthesized according to the procedures described for the preparation of Example **A3** (step **C** and **D**) by using ethyl (2S)-1-amino-2-methylcyclopropane-1-carboxylate hydrochloride in step **C**. LC-MS: m/z 488.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 7.22 - 7.15 (m, 2H), 7.16 - 7.09 (m, 2H), 7.05 - 7.00 (m, 1H), 6.76 (s, 1H), 6.62 - 6.51 (m, 3H), 6.39 (s, 1H), 4.36 - 4.35 (m, 3H), 3.73 (s, 6H), 3.12 - 3.04 (m, 2H), 2.89 - 2.82 (m, 2H), 2.01 (s, 3H), 1.94 - 1.45 (m, 2H), 1.15 -1.10 (m, 3H), 0.62 - 0.60 (m, 1H).

Example A8

1-({4'-acetyl-2-[(2,3-dihydro-1H-inden-2-yloxy) methyl]-3',5'-dimethoxy-[1,1'-biphenyl]-4-yl}amino)cyclopropane-1-carboxylic acid (Compound 121)

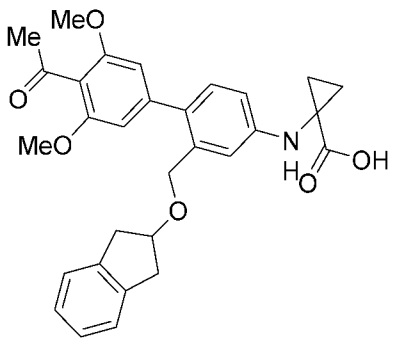


[0359] Step A: 1-[2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanone



8-1 **8-2**

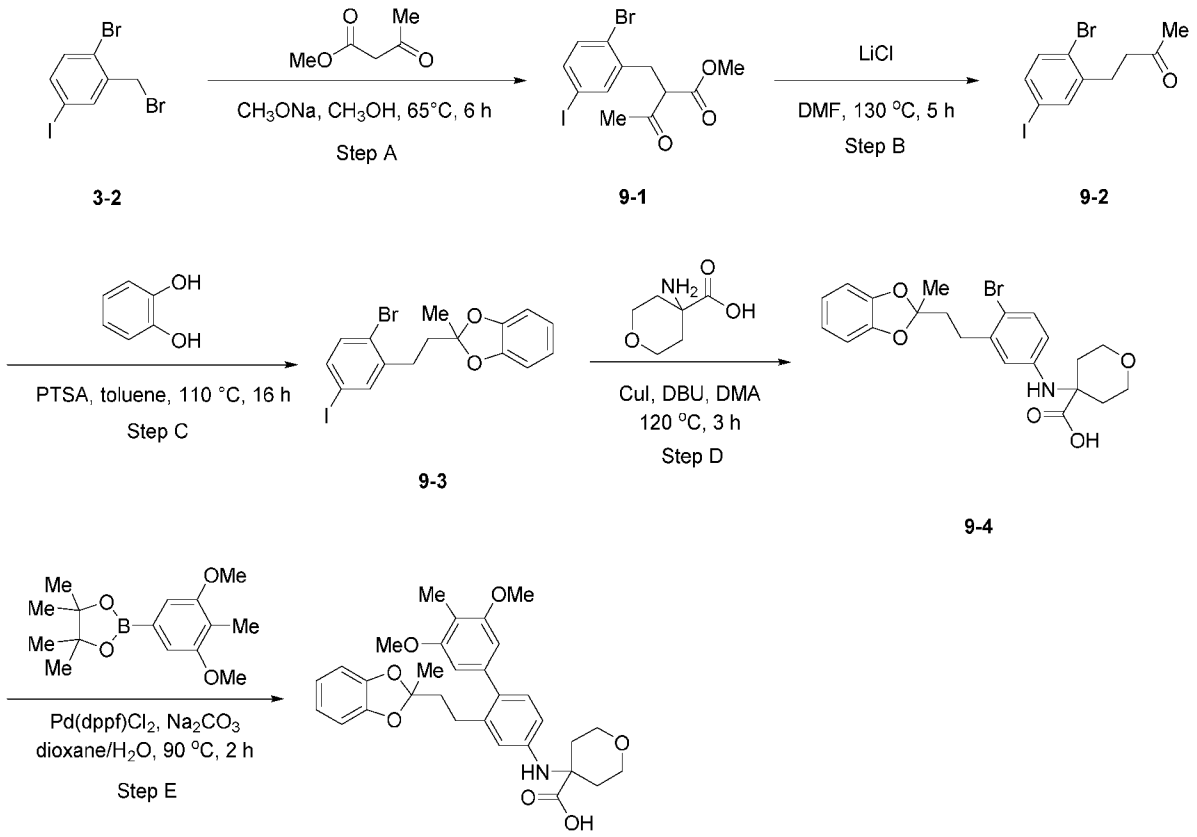
[0360] To a stirred mixture of 2',6'-dimethoxyacetophenone (1.00 g, 5.55 mmol), bis(pinacolato)diboron (1.69 g, 6.66 mmol) and 4,4'-Di-tert-butyl-2,2'-dipyridyl (dtbpy) (0.30 g, 1.11 mmol) in THF (10 mL), was added $[Ir(COD)(OMe)]_2$ (0.18 g, 0.28 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 16 h under nitrogen atmosphere. After cooling, the reaction mixture was diluted with water (30 mL), extracted with EtOAc (20 mL x3). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (3% to 7% MeOH in CH_2Cl_2) to afford 1-[2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanone (600 mg, 35.3%). LC-MS: m/z 306.9 $(M+H)^+$.



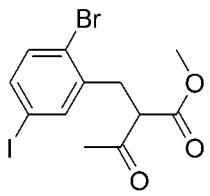
[0361] 1-({4'-acetyl-2-[(2,3-dihydro-1H-inden-2-yloxy) methyl]-3',5'-dimethoxy-[1,1'-biphenyl]-4-yl}amino)cyclopropane-1-carboxylic acid (**Compound 121**) was synthesized according to the procedures described for the preparation of Example **A3** (step **C** and **D**) by using 1-aminocyclopropane-1-carboxylic acid in step **C** and 1-[2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanone in step **D**. LC-MS: m/z 502.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 7.20 - 7.18 (m, 2H), 7.13 - 7.10 (m, 2H), 7.06 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 6.63 - 6.61 (m, 3H), 6.54 (s, 1H), 4.36 - 4.35 (m, 3H), 3.71 (s, 6H), 3.09 (dd, J = 16.4 Hz, 6.3 Hz, 2H), 2.85 (dd, J = 16.3 Hz, 3.7 Hz, 2H), 2.38 (s, 3H), 1.39 - 1.37 (m, 2H), 0.94 - 0.90 (m, 2H).

Example A9

4-({3',5'-dimethoxy-4'-methyl-2-[2-(2-methyl-1,3-benzodioxol-2-yl)ethyl]-[1,1'-biphenyl]- 4-yl}amino)oxane-4-carboxylic acid (Compound 132)



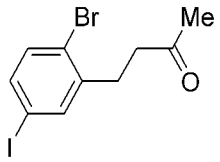
[0362] Step A: methyl 2-[(2-bromo-5-iodophenyl)methyl]-3-oxobutanoate



[0363] To the solution of methyl 3-oxobutanoate (927 mg, 7.99 mmol) in MeOH (20 mL) was added NaOMe (540 mg, 9.99 mmol). After being stirred for 10 min, to the mixture was added 1-bromo-2-(bromomethyl)-4-iodobenzene (2.5 g, 6.66 mmol). The resulting mixture was stirred for 6 h at 65 °C. After cooling, the mixture was poured into water (50 mL), extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and

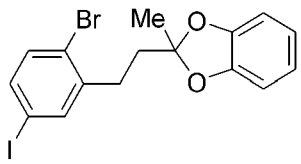
concentrated. The residue was purified by silica gel column (PE/EtOAc = 10/1) to afford methyl 2-(2-bromo-5-iodobenzyl)-3-oxobutanoate (1.7 g, 52.3% yield, 80% purity).

[0364] Step B: 4-(2-bromo-5-iodophenyl)butan-2-one

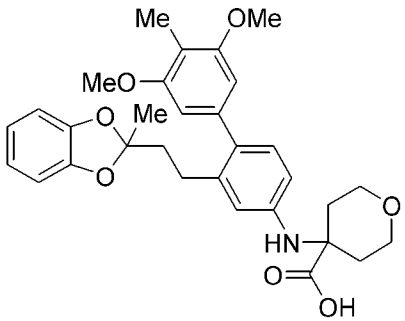


[0365] To the solution of methyl 2-[(2-bromo-5-iodophenyl)methyl]-3-oxobutanoate (700 mg, 1.70 mmol) in DMF (10 mL) were added lithium chloride (361 mg, 8.52 mmol) under nitrogen. The resulting mixture was stirred at 130 °C for 5 h. After cooling, the mixture was poured into water (50 mL), extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EtOAc= 10/1) to afford 4-(2-bromo-5- iodophenyl)butan-2-one (488 mg, 81.3% yield).

[0366] Step C: 2-[2-(2-bromo-5-iodophenyl)ethyl]-2-methyl-1,3-benzodioxole



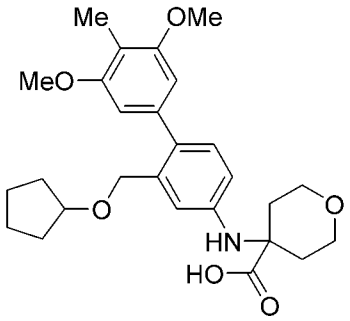
[0367] The mixture of 4-(2-bromo-5-iodophenyl)butan-2-one (550 mg, 1.56 mmol), catechol (858 mg, 7.79 mmol), PTSA (54 mg, 0.31 mmol) in toluene (10 ml) was stirred at 110 °C for 16 h. After cooling, the mixture was poured into water (50 mL), extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EA=10:1) to afford 2-[2-(2-bromo-5-iodophenyl)ethyl]-2-methyl-1,3-benzodioxole (110 mg, 15.9% yield).



[0368] 4-({3',5'-dimethoxy-4'-methyl-2-[2-(2-methyl-1,3-benzodioxol-2-yl)ethyl]-[1,1'-biphenyl] -4-yl}amino)oxane-4-carboxylic acid **(Compound 132)** was synthesized according to the procedures described for the preparation of Example **A3** (step **C** and **D**) by using 2-[2-(2-bromo-5-iodophenyl)ethyl]-2-methyl-1,3-benzodioxole in step **C**. LC-MS: m/z 534.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 6.90 (d, J = 8.3 Hz, 1H), 6.74 - 6.71 (s, 4H), 6.56 (s, 1H), 6.46 - 6.42 (m, 3H), 3.71 (s, 6H), 3.63 - 3.62 (m, 3H), 2.66 - 2.58 (m, 2H), 2.29 - 2.14 (m, 2H), 2.09 - 2.00 (m, 4H), 1.86 - 1.84 (m, 2H), 1.50 (s, 3H).

Example A10

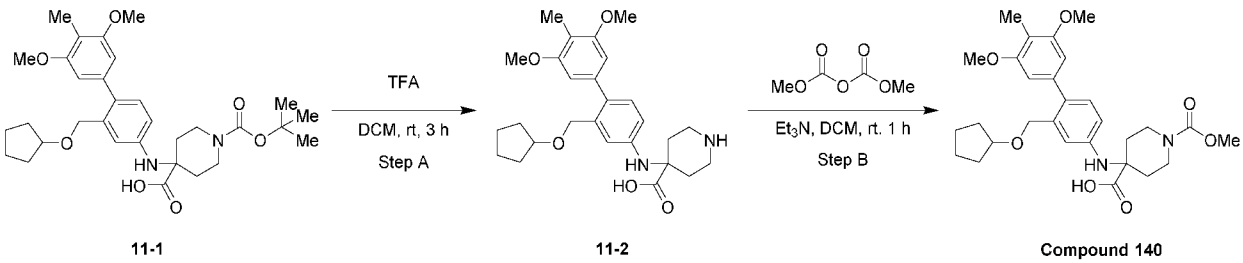
4-({2-[(cyclopentyloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl} amino)-oxane-4-carboxylic acid (Compound 134)



[0369] 4-({2-[(cyclopentyloxy)methyl]-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl}amino)-oxane-4-carboxylic acid **(Compound 134)** was synthesized according to the procedures described for the preparation of Example **A3** (step **B** to Step **D**) by using cyclopentanol in step **B**. LC-MS: m/z 470.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 6.98 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.54 - 6.52 (m, 3H), 4.19 (s, 2H), 3.91 - 3.90 (m, 1H), 3.76 (s, 6H), 3.65 - 3.57 (m, 4H), 2.04 - 2.00 (m, 5H), 1.99 - 1.87 (m, 2H), 1.69 - 1.53 (m, 6H), 1.46 - 1.44 (m, 2H).

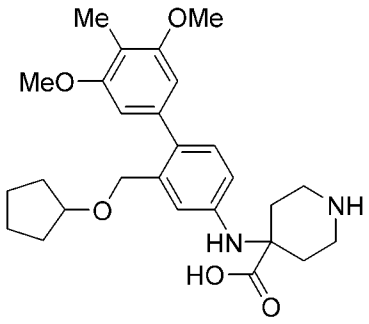
Example A11

4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl) amino) -1-(methoxycarbonyl)piperidine-4-carboxylic acid (Compound 140)



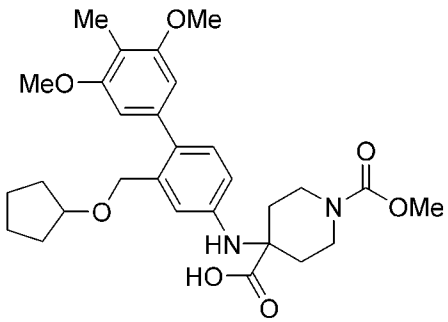
[0370] 1-(tert-butoxycarbonyl)-4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)piperidine-4-carboxylic acid **(11-1)** was synthesized according to the procedures described for the preparation of Example **A3** (step **B** to step **D**) by using cyclopentanol in step **B** and 4-amino-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid in step **C**. LC-MS: m/z 587.1 $(M+H_2O+H)^+$.

[0371] Step A: 4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)piperidine-4-carboxylic acid



[0372] The mixture of 1-(tert-butoxycarbonyl)-4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)piperidine-4-carboxylic acid (120 mg, 0.211 mmol) in TFA (2 mL) and CH_2Cl_2 (4 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under vacuum, the residue was purified by *prep*. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 60 mL/min; Gradient: 5% B to 60% B in 10 min) to afford 4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)piperidine-4-carboxylic acid (77 mg, 77.9% yield). LC-MS: m/z 469.1 $(M+H)^+$.

[0373] Step B: 4-((2-((cyclopentyloxy)methyl)-3'-hydroxy-5'-methoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)-1-(methoxycarbonyl)piperidine-4-carboxylic acid (**Compound 140**)

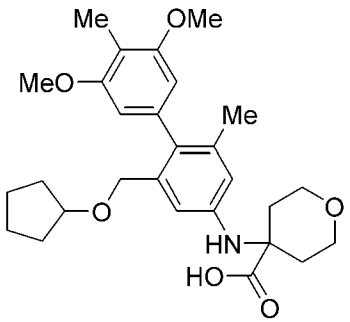


[0374] At 0 °C, to the solution of 4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)piperidine-4-carboxylic acid (60 mg, 0.13 mmol) and Et_3N (38.87 mg, 0.39 mmol)

in CH_2Cl_2 (3 mL) was added a solution of dimethyl dicarbonate (7.73 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) dropwise. After addition, the reaction mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. The crude was purified by *prep*. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 60 mL/min; Gradient: 5% B to 60% B in 8 min) to afford 4-((2-((cyclopentyloxy)methyl)-3'-hydroxy-5'-methoxy-4'-methyl-[1,1'-biphenyl]-4-yl) amino)-1-(methoxycarbonyl)piperidine-4-carboxylic (16.8 mg, 24.9% yield). LC-MS: m/z 527.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 6.96 (d, J = 8.4 Hz, 1H), 6.79 - 6.70 (m, 1H), 6.57 - 6.44 (m, 3H), 4.19 (s, 2H), 3.96 - 3.86 (m, 1H), 3.76 (s, 6H), 3.68 - 3.50 (m, 5H), 3.30 - 3.20 (m, 2H), 2.00 (s, 3H), 1.97 - 1.84 (m, 4H), 1.68 - 1.53 (m, 6H), 1.49 - 1.38 (m, 2H).

Example A12

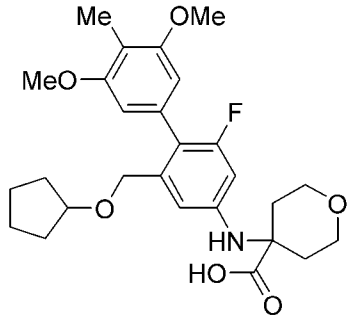
4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4',6-dimethyl-[1,1'-biphenyl]-4-yl)amino) tetrahydro-2H-pyran-4-carboxylic acid (Compound 141)

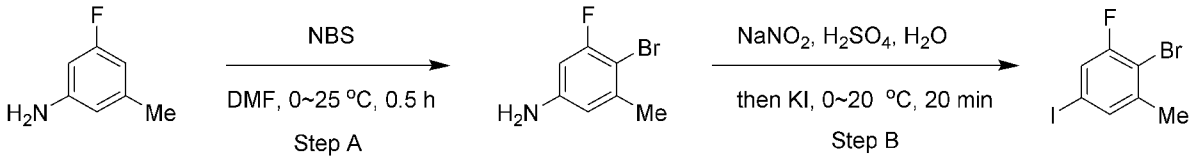


[0375] 4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4',6-dimethyl-[1,1'-biphenyl]-4-yl)amino) tetrahydro-2H-pyran-4-carboxylic acid **(Compound 141)** was synthesized according to the procedures described for the preparation of Example **A3** (step **A** to step **D**) by using 2-bromo-5-iodo-1,3-dimethylbenzene in step **A** and cyclopentanol in step **B**. LC-MS: m/z 484.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 6.57 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 6.33 (s, 2H), 3.96 (s, 2H), 3.76 - 3.74 (m, 1H), 3.69 (s, 6H), 3.68 - 3.54 (m, 4H), 2.09 - 1.93 (m, 5H), 1.88 - 1.80 (m, 5H), 1.66 - 1.47 (m, 4H), 1.47 - 1.33 (m, 4H).

Example A13

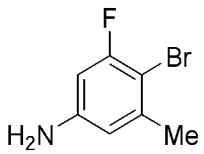
4-((2-((cyclopentyloxy)methyl)-6-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 147)





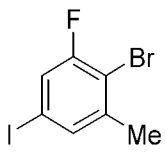
13-1 **13-2** **13-3**

[0376] Step A: 4-bromo-3-fluoro-5-methylaniline

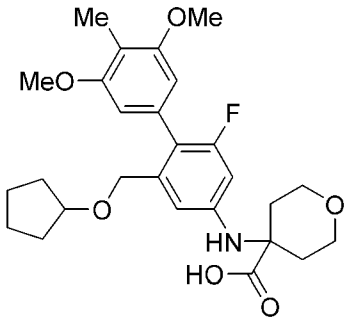


[0377] To the mixture of 3-fluoro-5-methyl-aniline (5 g, 40.0 mmol) in DMF (40 mL) was added NBS (7.25 g, 40.8 mmol) at 0 °C. The mixture was stirred at 25 °C for 0.5 h. The reaction was quenched with H_2O (20 mL). The mixture was extracted with EtOAc (30 mL x 3). The combined organic layer was washed with H_2O (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel column (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc /PE gradient at 85 mL/min) to give 4-bromo-3-fluoro-5-methyl-aniline (8.0 g, 98.1% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H), 6.32 - 6.28 (m, 1H), 2.31 (s, 3H).

[0378] Step B: 2-bromo-1-fluoro-5-iodo-3-methylbenzene



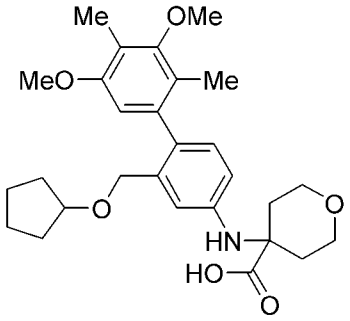
[0379] To a solution of 4-bromo-3-fluoro-5-methyl-aniline (21.7 g, 106 mmol) in MeCN (500 mL) was added a solution of H_2SO_4 (14.0 mL, 263 mmol) in H_2O (30 mL) at 0 °C. After being stirred for 5 minutes, a solution of $NaNO_2$ (14.7 g, 213 mmol) in water (30 mL) was added dropwise, and the reaction mixture was stirred for an additional 15 minutes at 0 °C. Then a solution of KI (70.6 g, 425 mmol) in water (60 mL) was added. After addition, the ice-bath was removed and warmed up to 25 °C, the resulting reaction mixture was stirred for an additional 20 minutes. The mixture was quenched with *sat. aq.* $Na_2S_2O_3$ aqueous, diluted with water (300 mL), extracted with EtOAc (160 mL x2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel column (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0 % EtOAc/PE gradient at 100 mL/min) to give 2-bromo-1-fluoro-5-iodo-3-methyl-benzene (31.6 g, 94.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.30 - 7.26 (m, 1H), 2.38 (s, 3H).

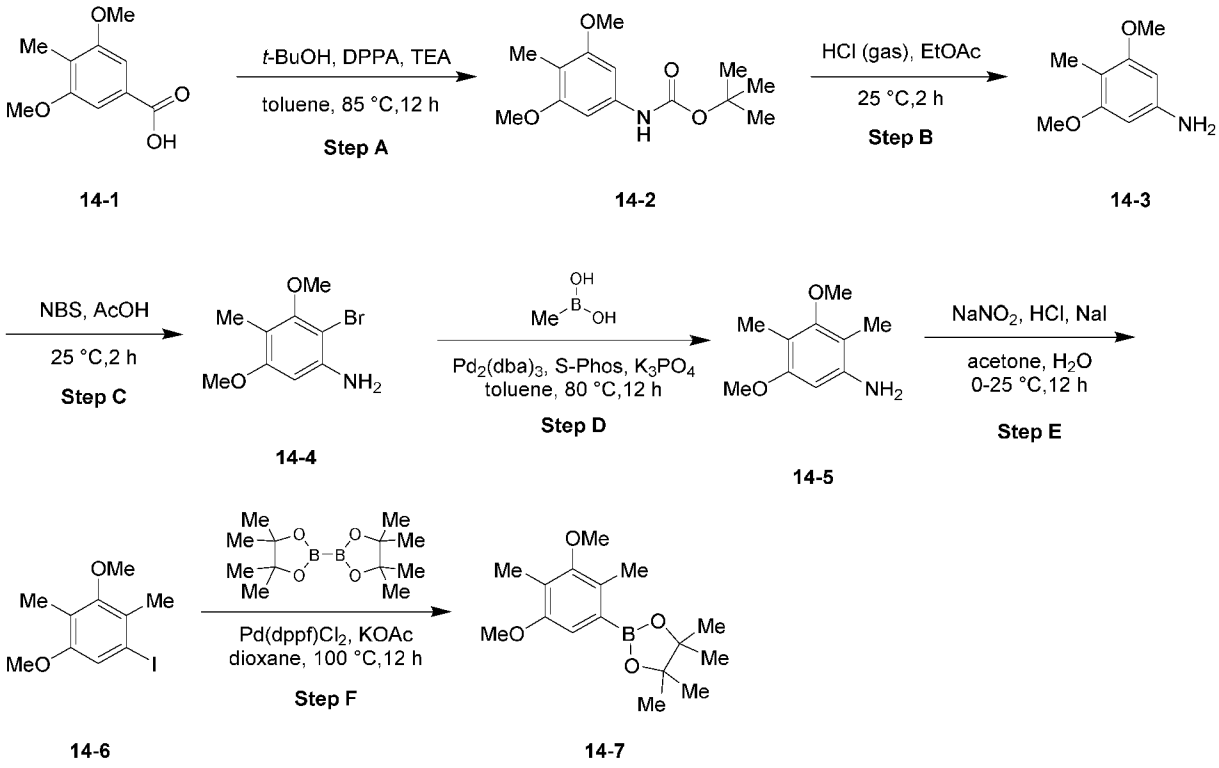


[0380] 4-((2-((cyclopentyloxy)methyl)-6-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (**Compound 147**) was synthesized according to the procedures described for the preparation of Example **A3** (step **A** and **D**) by using 2-bromo-1-fluoro-5-iodo-3-methylbenzene in step **A** and cyclopentanol in step **B**. LC-MS: m/z 488.4 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 6.65 (s, 1H), 6.46 (s, 2H), 6.39 (d, J = 12.0 Hz, 1H), 4.18 (s, 2H), 3.87 - 3.74 (m, 11H), 2.28 - 2.20 (m, 2 H), 2.09 (s, 3H), 2.06 - 2.01 (m, 2H), 1.66 - 1.50 (m, 8H).

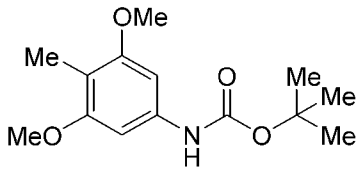
Example A14

4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-2',4'-dimethyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 148)



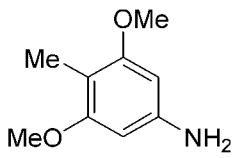


[0381] Step A: tert-butyl (3,5-dimethoxy-4-methylphenyl)carbamate



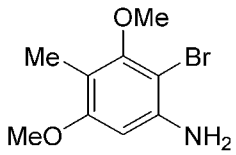
[0382] To a solution of 3,5-dimethoxy-4-methylbenzoic acid (25 g, 127.42 mmol) in toluene (70 mL) and *t*-BuOH (70 mL) was added TEA (39 mL, 280.20 mmol) and DPPA (38.10 g, 138.44 mmol). After being degassed and purged with nitrogen for 3 times, the resulting mixture was stirred at 85 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (200 mL x3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EtOAc = 9/2) to give tert-butyl (3,5-dimethoxy-4-methylphenyl)carbamate (28.86 g, 79.9% yield). LC-MS: m/z 268.1 $(M+H)^+$.

[0383] Step B: 3,5-dimethoxy-4-methylaniline



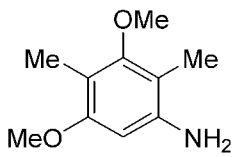
[0384] The mixture of tert-butyl (3,5-dimethoxy-4-methylphenyl)carbamate (28.86 g, 107.96 mmol) in 4 M HCl (gas)/EtOAc (258 mL) was stirred at 25 °C for 2 h. Then *p*H value was adjusted to 8 - 9 with *sat. aq.* $NaHCO_3$, the mixture was extracted with EtOAc (200 mL x3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give 3,5-dimethoxy-4-methylaniline (18.03 g, 99.9% yield).

[0385] Step C: 2-bromo-3,5-dimethoxy-4-methylaniline



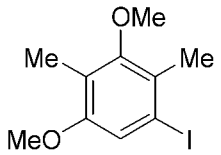
[0386] To a solution of 3,5-dimethoxy-4-methylaniline (5 g, 29.90 mmol) in AcOH (20 mL) was added NBS (5.32 g, 29.90 mmol) and the mixture was stirred at 25 °C for 2 h. Then the *p*H value was adjusted to 8 - 9 with *sat. aq.* $NaHCO_3$, the mixture was extracted with EtOAc (50 mL x3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (PE/EtOAc = 9/1) to give 2-bromo-3,5-dimethoxy-4-methylaniline (4.59 g, 56.3% yield). LC-MS: m/z 246.1 $(M+H)^+$.

[0387] Step D: 3,5-dimethoxy-2,4-dimethylaniline



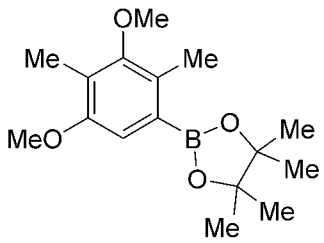
[0388] To a solution of 2-bromo-3,5-dimethoxy-4-methylaniline (4.59 g, 18.65 mmol) in toluene (30 mL) was added methylboronic acid (2.79 g, 46.63 mmol), K_3PO_4 (15.84 g, 74.60 mmol), S-Phos (1.53 g, 3.73 mmol) and $Pd_2(dba)_3$ (1.71 g, 1.87 mmol) under nitrogen. After being degassed and purged with nitrogen for 3 times. Then the mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. After cooling and filtered, the filtrate was concentrated. The residue was purified by silica gel column (PE/EtOAc = 9/1) to give 3,5-dimethoxy-2,4-dimethylaniline (2.45 g, 72.5% yield). LC-MS: m/z 182.2 $(M+H)^+$.

[0389] Step E: 1-iodo-3,5-dimethoxy-2,4-dimethylbenzene



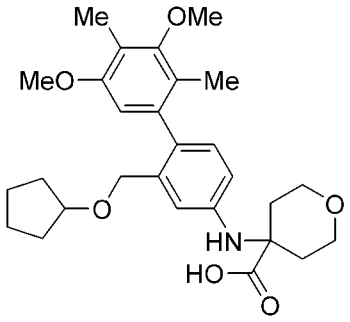
[0390] To a solution of 3,5-dimethoxy-2,4-dimethylaniline (2.25 g, 12.42 mmol) in 37% HCl (12 mL, 124.15 mmol) and acetone (15 mL) was added a solution of $NaNO_2$ (2.14 g, 31.04 mmol) in H_2O (5 mL) at 0 °C and the mixture was stirred at 0 °C for 0.5 h. A solution of NaI (7.44 g, 49.66 mmol) in H_2O (5 mL) was added and the mixture was stirred at 25 °C for 16 h. The reaction was quenched with H_2O (30 mL), extracted with EtOAc (30 mL x3). The combined organic layer was concentrated and purified by silica gel column (100% PE) to give the red crude product. The crude was dissolved in EtOAc (40 mL) and the mixture was washed with *sat. aq.* $Na_2S_2O_3$ solution (30 mL x3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give 1-iodo-3,5-dimethoxy-2,4-dimethylbenzene (2.64 g, 71.6% yield). LC-MS: m/z 292.9 $(M+H)^+$.

[0391] Step F: 2-(3,5-dimethoxy-2,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0392] To a solution of 1-iodo-3,5-dimethoxy-2,4-dimethylbenzene (1 g, 3.42 mmol) in 1,4-dioxane (20 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.74 g, 6.85 mmol), KOAc (1.01 g, 10.27 mmol) and $Pd(dppf)Cl_2$ (250.49 mg, 342.33 μmol). After being degassed and purged with nitrogen for 3 times, the reaction mixture was stirred at 100 °C for 12 h under nitrogen. After cooling, the reaction mixture was filtered, the filtrate was concentrated. The residue was purified by silica gel column

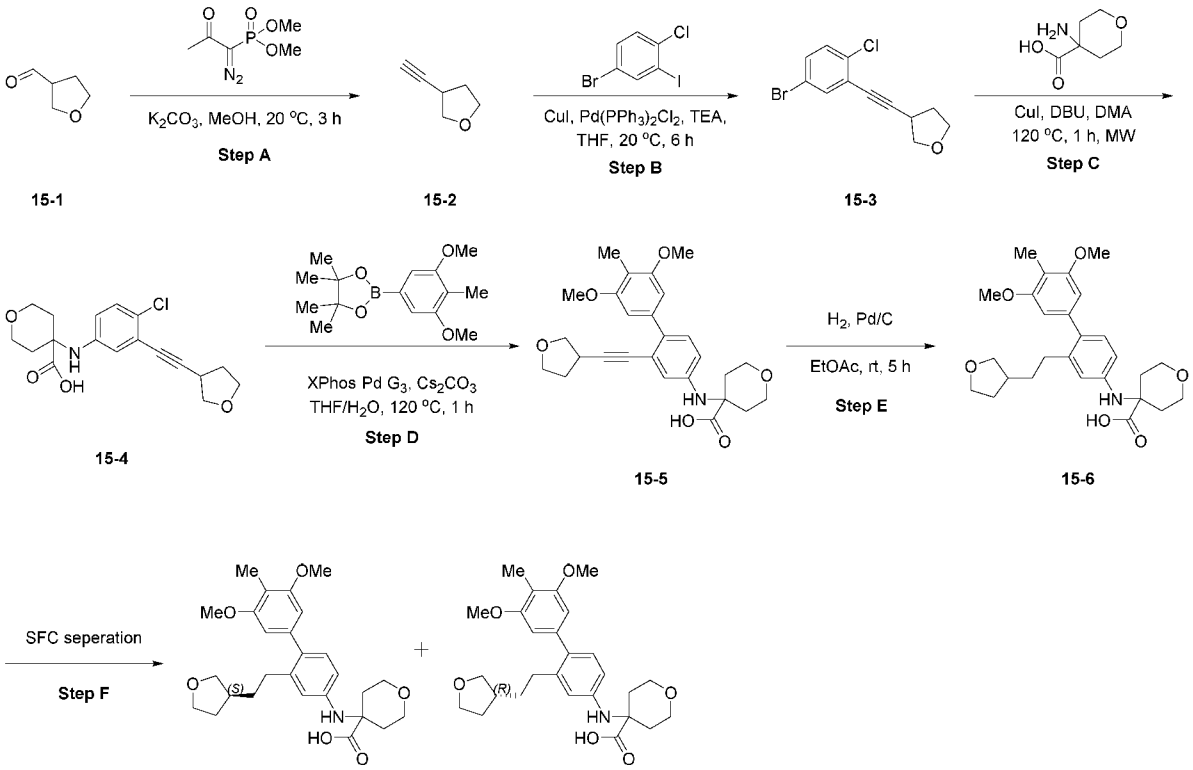
(PE/EtOAc = 32/1) to give 2-(3,5-dimethoxy-2,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (404 mg, 40.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 3.77 (s, 3H), 3.60 (s, 3H), 2.35 (s, 3H), 2.10 (s, 3H), 1.27(s, 12H).



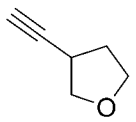
[0393] 4-((2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-2',4'-dimethyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (**Compound 148**) was synthesized according to the procedures described for the preparation of Example **A3** (step **A** and **D**) by using cyclopentanol in step **B** and 2-(3,5-dimethoxy-2,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in step **D**. LC-MS: m/z 484.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 6.87 - 6.80 (m, 2H), 6.68 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.47 (s, 1H), 4.14 - 4.02 (m, 2H), 3.88 - 3.77 (m, 5H), 3.76 (s, 3H), 3.71 (s, 3H), 2.30 - 2.20 (m, 2H), 2.16 (s, 3H), 2.05 - 1.95 (m, 2H), 1.90 (s, 3H), 1.63 - 1.39 (m, 8H).

Example A15

(S)-4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid and (R)-4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compounds 185 and 186)

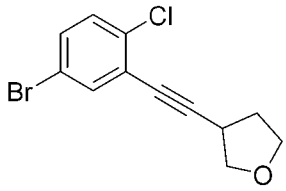


[0394] Step A: 3-ethynyltetrahydrofuran



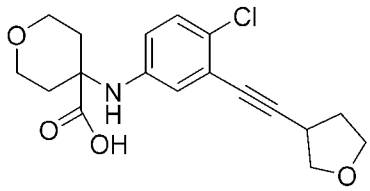
[0395] To a mixture of tetrahydrofuran-3-carbaldehyde (5.0 g, 49.9 mmol), K_2CO_3 (10.0 g, 72.4 mmol) in MeOH (60 mL) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (10.6 g, 54.9 mmol). The reaction mixture was stirred at 20 °C for 3 h. The suspension was filtered through a pad of Celite® and the pad washed with petroleum ether (30 mL), the filtrate was concentrated in vacuo (the bath temperature below 15 °C) to give the 3-ethynyltetrahydrofuran (10 g, crude), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (t, J = 7.8 Hz, 1H), 3.97 - 3.80 (m, 2H), 3.67 (dd, J = 8.0 Hz, 7.2 Hz, 1H), 3.07 - 2.93 (m, 1H), 2.30 - 2.16 (m, 1H), 2.12 (d, J = 2.2 Hz, 1H), 2.05 - 1.97 (m, 1H).

[0396] Step B: 3-((5-bromo-2-chlorophenyl)ethynyl)tetrahydrofuran



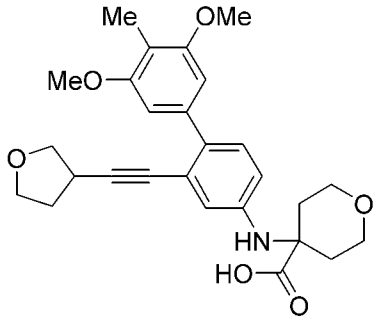
[0397] A mixture of CuI (50.0 mg, 263 μmol), $Pd(PPh_3)_2Cl_2$ (92.2 mg, 131 μmol) and TEA (3.99 g, 39.4 mmol) in THF (100 mL) was degassed and purged with nitrogen for 3 times, and then 4-bromo-1-chloro-2-iodobenzene (5.00 g, 15.8 mmol), 3-ethynyltetrahydrofuran (10.0 g, 104 mmol) was added. The resulting mixture was stirred at 20 °C for 6 h under nitrogen atmosphere. The reaction mixture was diluted with *sat. aq.* NH_4Cl (40 mL), extracted with ethyl acetate (40 mL x 2). The combined organic layer was washed with brined (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0 ~15 % EtOAc/PE gradient at 60 mL/min) to afford 3-((5-bromo-2-chlorophenyl)ethynyl)tetrahydrofuran (1.5 g, 40.0% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 7.26 -7.22 (m, 1H), 4.10 (t, J = 7.8 Hz, 1H), 4.02 - 3.86 (m, 2H), 3.78 - 3.76 (m, 1H), 3.31 - 3.20 (m, 1H), 2.37 - 2.25 (m, 1H), 2.18 - 2.05 (m, 1H).

[0398] Step C: 4-((4-chloro-3-((tetrahydrofuran-3-yl)ethynyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid



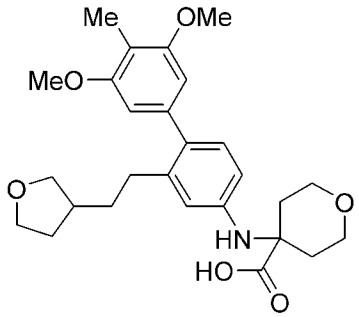
[0399] The mixture of 3-((5-bromo-2-chlorophenyl)ethynyl)tetrahydrofuran (1 g, 3.50 mmol), 4-aminotetrahydro-2H-pyran-4-carboxylic acid (1.02 g, 7.00 mmol), CuI (133 mg, 700.37 μmol) and DBU (1.33 g, 8.75 mmol, 1.32 mL) in DMA (10 mL) was heated at 120 °C for 60 min under microwave. The reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was diluted with brine (50 mL), extracted with EtOAc (50 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 0~50% EtOAc/PE gradient) to give 4-((4-chloro-3-((tetrahydrofuran-3-yl)ethynyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (450 mg, 1.29 mmol). LC-MS: m/z 349.8 $(M+H)^+$.

[0400] Step D: 4-((3',5'-dimethoxy-4'-methyl-2-((tetrahydrofuran-3-yl)ethynyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid



[0401] To a solution of 4-((4-chloro-3-((tetrahydrofuran-3-yl)ethynyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (400 mg, 1.14 mmol) and 2-(3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (636 mg, 2.29 mmol) in THF (4 mL) and H_2O (4 mL) was added XPhos Pd G3 (96.8 mg, 114 μmol) and Cs_2CO_3 (745 mg, 2.29 mmol). The mixture was stirred at 120 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was diluted with brine (50 mL), acidified with 1N HCl to *p*H = 5, extracted with EtOAc (50 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 0~50% EtOAc/PE gradient) to give 4-((3',5'-dimethoxy-4'-methyl-2-((tetrahydrofuran-3-yl)ethynyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (470 mg, 1.01 mmol). LC-MS: m/z 465.9 $(M+H)^+$.

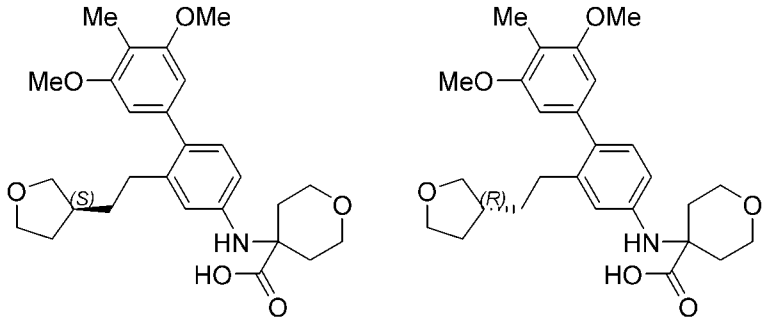
[0402] Step E: 4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid



[0403] To a solution of 4-((3',5'-dimethoxy-4'-methyl-2-((tetrahydrofuran-3-yl)ethynyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (470 mg, 1.01 mmol) in EtOAc (0.5 mL) was added 10% Pd/C (100 mg). The reaction mixture was stirred under H_2 atmosphere (15 psi) at 25 °C for 5 h. The mixture was diluted with EtOAc (20 mL) filtered and evaporated. The residue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 0~40% EtOAc/PE gradient) to give 4-

((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (90 mg, 19.0% yield, 80% purity). LC-MS: m/z 470.3 $(M+H)^+$.

[0404] Step F: (S)-4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid and (R)-4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 185 and 186)



[0405] Sample of 4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid was subjected to SFC separation (column: DAICEL CHIRALPAK AD (250mm*30mm,10μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in EtOH]; B%: 20%-20%). After removal of the solvent, the samples were lyophilized to provide the title compounds. The absolute stereochemistry of each product was not identified.

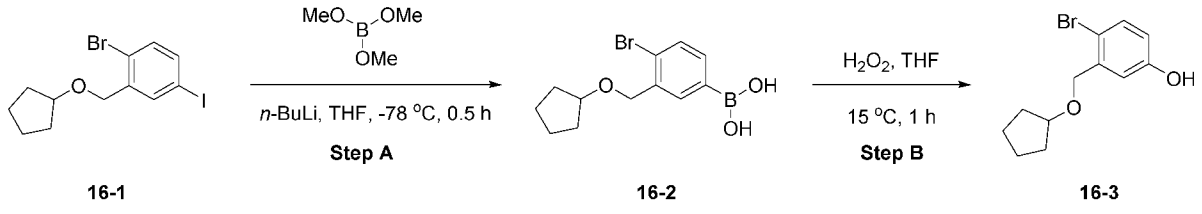
[0406] Enantiomer 1 4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 185)** SFC analysis condition: Column: ChiralPak AD-3 150×4.6mm I.D., 3 um; Mobile phase: A: CO_2 B: ethanol (0.05% diethylamine); Isocratic: 15% B, Flow rate: 2.5 mL/min; Column temp.: 40 °C, Retention time: 3.908 min. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 6.84 (d, J = 8.2 Hz, 1H), 6.55 (s, 1H), 6.48 - 6.41 (m, 3H), 3.73 (s, 6H), 3.64 - 3.61 (m, 6H), 3.52 - 3.51 (m, 2H), 3.09 - 3.04 (m, 1H), 2.42 - 2.40 (m, 1H), 2.05 - 1.97 (m, 7H), 1.88 - 1.76 (m, 3H), 1.49 - 1.44 (m, 2H). LC-MS: m/z 470.3 $(M+H)^+$.

[0407] Enantiomer 2 4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 186)** SFC analysis condition: Column: ChiralPak AD-3 150×4.6mm I.D., 3 um; Mobile phase: A: CO_2 B: ethanol (0.05% diethylamine); Gradient: from 5% to 40% of B in 4.5 min, then 5% of B for 1.5 min, Flow rate: 2.5 mL/min; Column temp.: 40 °C, Retention time: 3.827 min. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 6.86 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 6.45 - 6.40 (m, 3H), 3.73 (s, 6H), 3.65 - 3.60 (m, 6H), 3.53 - 3.49 (m, 2H), 3.09 - 3.04 (m,

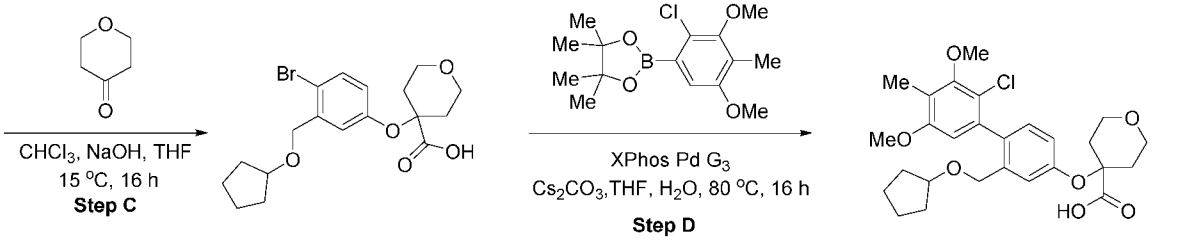
1H), 2.44 - 2.37 (m, 1H), 2.06 - 1.94 (m, 7H), 1.89 - 1.77 (m, 3H), 1.50 - 1.44 (m, 2H). LC-MS: m/z 470.3 $(M+H)^+$.

Example A16

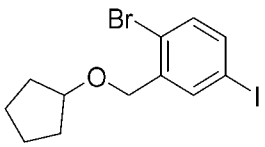
4-((2'-chloro-2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)tetrahydro-2H-pyran-4-carboxylic acid (Compound 192)



16-1 16-2 16-3

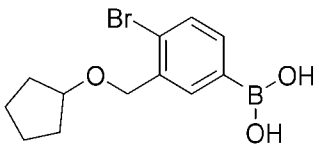


16-4 Compound 192



[0408] 1-bromo-2-(cyclopentoxymethyl)-4-iodo-benzene (**16-1**) was synthesized according to the procedures described for the preparation of Example **A3** (step **A** to step **B**) by using cyclopentanol in step **B**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 2.0 Hz, 1H), 7.44 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 4.45 (s, 2H), 4.10 - 4.02 (m, 1H), 1.85 - 1.52 (m, 8H).

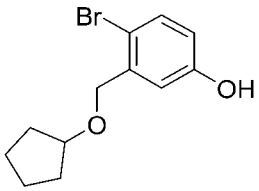
[0409] Step A: (4-bromo-3-((cyclopentyloxy)methyl)phenyl)boronic acid



[0410] At -78 °C, *n*-BuLi (2.5 M, 1.3 mL) was added into the mixture of 1-bromo-2-(cyclopentoxymethyl)-4-iodo-benzene (1.2 g, 3.2 mmol) in THF (10 mL) under nitrogen atmosphere.

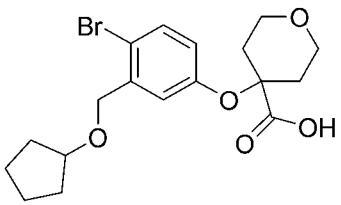
After being stirred for 0.5 h, trimethyl borate (356 μL, 3.2 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 0.5 h and 15 °C for 0.5 h. Then it was quenched with 2N HCl (15 mL), extracted with ethyl acetate (30 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the crude [4-bromo-3-(cyclopentoxymethyl)phenyl]boronic acid (1 g, crude) as a brown solid, which used in the next step without purification.

[0411] Step B: 4-bromo-3-((cyclopentyloxy)methyl)phenol



[0412] To the mixture of [4-bromo-3-(cyclopentoxymethyl)phenyl]boronic acid (1 g, 3.3 mmol) in THF (10 mL) was added 30% H_2O_2 (10 mL, 104.1 mmol). The resulting mixture was stirred at 15 °C for 1 h. The reaction mixture was quenched with *sat. aq.* Na_2SO_3 (50 mL) carefully, extracted with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to give 4-bromo-3-(cyclopentoxymethyl)phenol (360 mg, 39.7% yield). LC-MS: m/z 269.1 $(M-H)^-$.

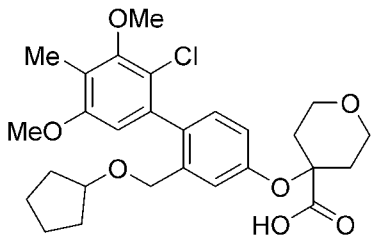
[0413] Step C: 4-(4-bromo-3-((cyclopentyloxy)methyl)phenoxy)tetrahydro-2H-pyran-4-carboxylic acid



[0414] At 0 °C, to the mixture of 4-bromo-3-(cyclopentoxymethyl)phenol (360 mg, 1.3 mmol) in THF (6 mL) were added NaOH (266 mg, 6.6 mmol) and tetrahydropyran-4-one (399 mg, 4.0 mmol, 366 μL). Subsequently, $CHCl_3$ (536 μL, 6.6 mmol) was added dropwise. The resulting mixture was stirred at 15 °C for 16 h. The reaction mixture was acidified with 1N HCl (~3 mL), extracted with ethyl acetate (15 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/PE gradient at 40mL/min) to give 4-[4-bromo-3-(cyclopentoxymethyl)phenoxy]tetrahydropyran-4-carboxylic acid (280 mg, 52.8% yield). ^1H NMR (400

MHz, $CDCl_3$) δ 7.37 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 6.68 (dd, J = 8.8, 3.2 Hz, 1H), 4.44 (s, 2H), 4.04 - 3.98 (m, 1H), 3.82 - 3.76 (m, 4H), 2.26 - 2.13 (m, 4H), 1.77 - 1.53 (m, 8H).

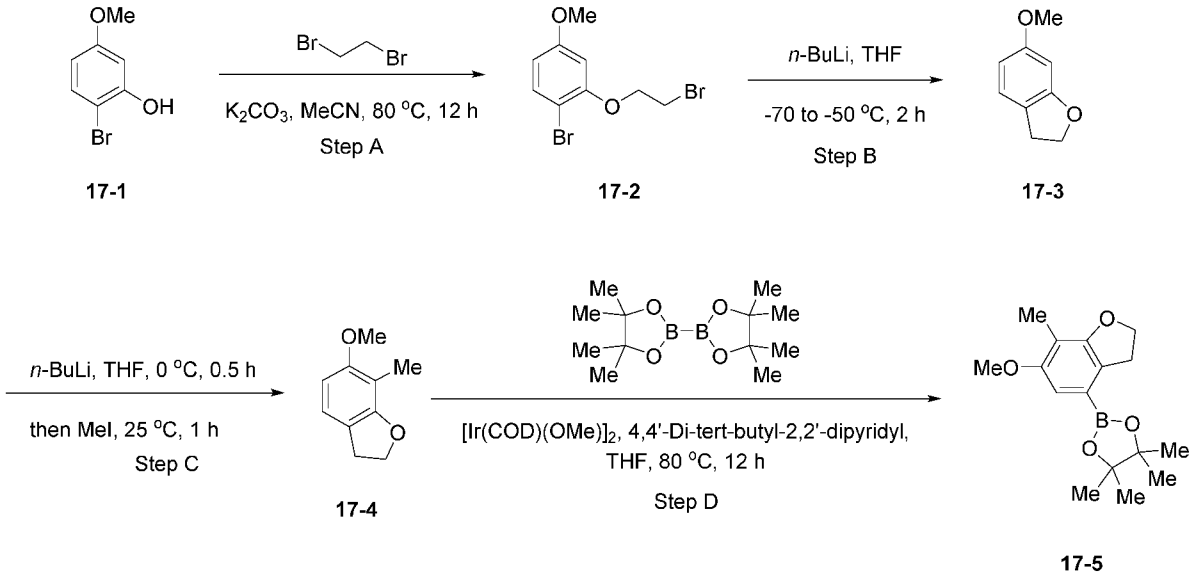
[0415] Step D: 4-((2'-chloro-2-((cyclopentyloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 192)**



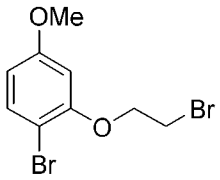
[0416] To the mixture of 4-[4-bromo-3-(cyclopentoxymethyl)phenoxy]tetrahydropyran-4-carboxylic acid (220 mg, 551 μmol) and 2-(2-chloro-3,5-dimethoxy-4-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (189 mg, 606 μmol) in THF (3 mL) and H_2O (3 mL) was added XPhos Pd G3 (46.6 mg, 55.1 μmol) and Cs_2CO_3 (359 mg, 1.1 mmol). The resulting mixture was stirred at 80 °C under nitrogen for 16 h. After cooling, the reaction mixture was acidified by 1N HCl to pH = 4. The mixture was extracted with ethyl acetate (10 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% EtOAc/PE gradient at 40 mL/min) and further purified by *prep*. HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (0.05% $NH_3 \cdot H_2O$+10 mM NH_4HCO_3)-CH_3CN]; B%: 35%-65%, 7 min) to give 4-[4-(2-chloro-3,5-dimethoxy-4-methyl-phenyl)-3-(cyclopentoxymethyl)phenoxy]tetrahydropyran-4-carboxylic acid (70.3 mg, 25.3% yield). LC-MS: m/z 522.2 $(M+NH_3+H)^+$.^{1}H NMR (400 MHz, CD_3OD) δ 7.10 (d, J = 2.8 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.4 Hz, 2.8 Hz, 1H), 6.62 (s, 1H), 4.92 (s, 14H), 4.20 (dd, J = 28.4 Hz, 12 Hz, 1H), 3.87 - 3.77 (m, 11H), 2.33 - 2.09 (m, 7H), 1.70 - 1.39 (m, 8H).

Example A17

4-((3-((cyclopentyloxy)methyl)-4-(6-methoxy-7-methyl-2,3-dihydrobenzofuran-4-yl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 193)

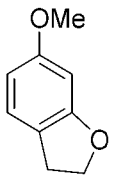


[0417] Step A: 1-bromo-2-(2-bromoethoxy)-4-methoxy-benzene



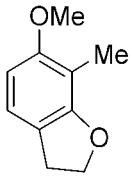
[0418] To a solution of 2-bromo-5-methoxy-phenol (7.3 g, 36 mmol) and 1,2-dibromoethane (34 g, 180 mmol) in MeCN (150 mL) was added K_2CO_3 (7.45 g, 54 mmol). The mixture was stirred at 80 °C for 12 h. After cooling, the mixture was diluted with water (100 mL), extracted with ethyl acetate (120 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~2% EtOAc/PE gradient at 100 mL/min) to give 1-bromo-2-(2-bromoethoxy)-4-methoxy-benzene (7.2 g, 64.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.6 Hz, 1H), 6.52 - 6.40 (m, 2H), 4.30 (t, J = 6.4 Hz, 2H), 3.79 (s, 3H), 3.67 (t, J = 6.4 Hz, 2H).

[0419] Step B: 6-methoxy-2,3-dihydrobenzofuran



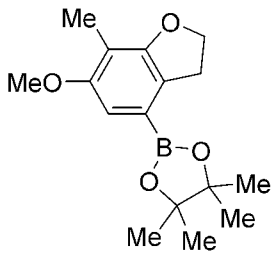
[0420] To a solution of 1-bromo-2-(2-bromoethoxy)-4-methoxy-benzene (7.2 g, 23.2 mmol) in THF (60 mL) was added *n*-BuLi (2.5 M, 10.22 mL) dropwise at -70 °C. The reaction mixture was stirred at -70 °C for 1 h and then -50 °C for 2 h. The mixture was quenched with *sat. aq.* NH_4Cl (60 mL), extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~3% EtOAc/PE gradient at 100 mL/min) to give 6-methoxy-2,3-dihydrobenzofuran (1.08 g, 31.0 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 - 6.91 (m, 1H), 6.32 - 6.31 (m, 2H), 4.48 (t, J = 8.6 Hz, 2H), 3.67 (s, 3H), 3.04 (t, J = 8.6 Hz, 2H).

[0421] Step C: 6-methoxy-7-methyl-2,3-dihydrobenzofuran

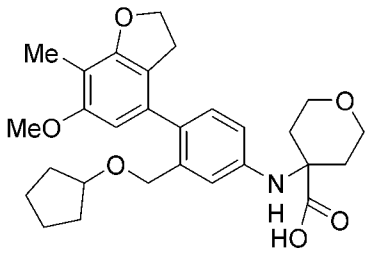


[0422] To a solution of 6-methoxy-2,3-dihydrobenzofuran (1.08 g, 7.19 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M, 3.16 mL) dropwise at 80 °C. After being stirred for 0.5 h, MeI (1.22 g, 8.63 mmol) was added dropwise. The resulting mixture was stirred at 25 °C for 1 h. Then the mixture was diluted with water (20 mL), extracted with ethyl acetate (30 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~2% EtOAc/PE gradient at 80 mL/min) to give 6-methoxy-7-methyl-2,3-dihydrobenzofuran (192 mg, 16.3% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, J = 8.0 Hz, 1H), 6.28 (d, J = 8.4 Hz, 2H), 4.49 (t, J = 8.6 Hz, 2H), 3.72 (s, 3H), 3.08 (t, J = 8.6 Hz, 2H), 2.01 (s, 3H).

[0423] Step D: 2-(6-methoxy-7-methyl-2,3-dihydrobenzofuran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



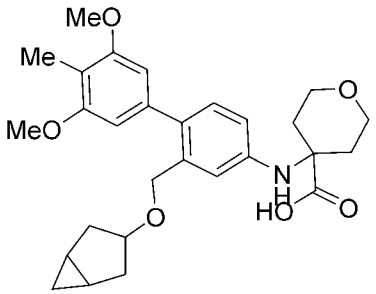
[0424] To a solution of 6-methoxy-7-methyl-2,3-dihydrobenzofuran (192 mg, 1.17 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (267 mg, 1.05 mmol) in THF (5 mL) was added $[Ir(COD)(OMe)]_2$ (3.88 mg, 5.85 μmol) and 4,4'-Di-tert-butyl-2,2'-dipyridyl (dtbpy) (3.14 mg, 11.7 μmol). The reaction mixture was stirred at 80 °C for 12 h. The mixture was evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~3% EtOAc/PE gradient at 80 mL/min) to give 2-(6-methoxy-7-methyl-2,3-dihydrobenzofuran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (129 mg, 38.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 4.48 (t, J = 8.8 Hz, 2H), 3.77 (s, 3H), 3.25 (t, J = 8.8 Hz, 2H), 2.03 (s, 3H), 1.25 (s, 12H).



[0425] 4-((3-((cyclopentyloxy)methyl)-4-(6-methoxy-7-methyl-2,3-dihydrobenzofuran-4-yl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 193)** was synthesized according to the procedures described for the preparation of Example **A3** (step **A** and **D**) by using cyclopentanol in step **B** and 2-(6-methoxy-7-methyl-2,3-dihydrobenzofuran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in step **D**. LC-MS: m/z 482.3 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 6.94 (d, J = 8.2 Hz, 1H), 6.78 (s, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.23 (s, 1H), 4.47 (t, J = 8.4 Hz, 2H), 4.20 (s, 2H), 3.89 - 3.75 (m, 5H), 3.74 (s, 3H), 2.89 (t, J = 8.0 Hz, 2H), 2.27 - 2.16 (m, 2H), 2.03 - 1.90 (m, 5H), 1.65 - 1.47 (m, 8H).

Example A18

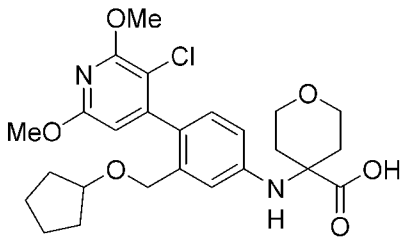
4-((2-((bicyclo[3.1.0]hexan-3-yloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 182)

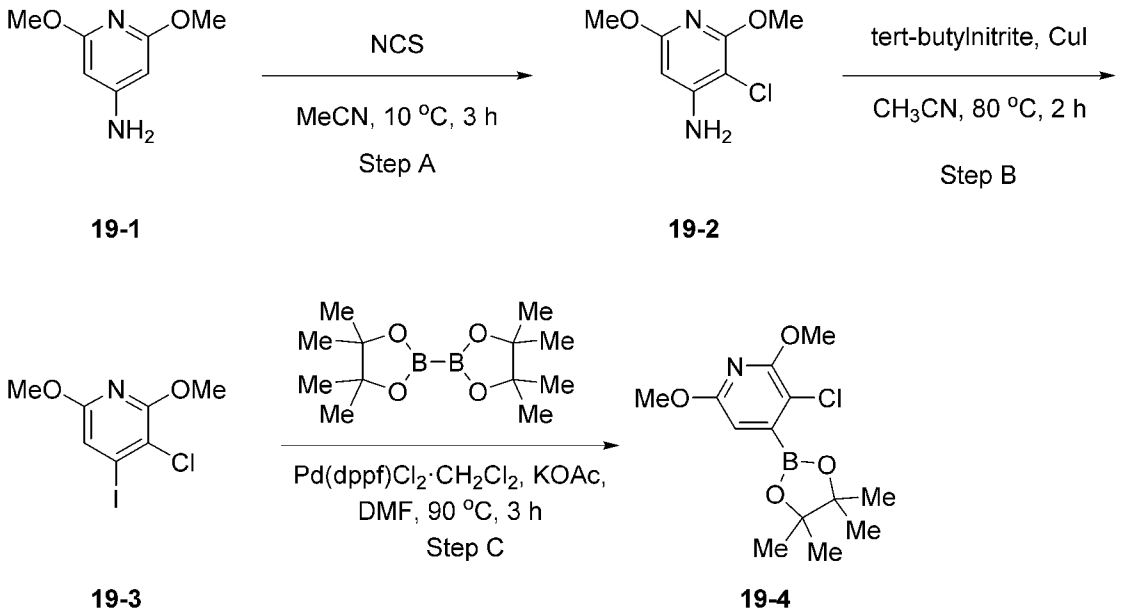


[0426] 4-((2-((bicyclo[3.1.0]hexan-3-yloxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 182)** was synthesized according to the procedures described for the preparation of Example **A3** (step **B** to Step **D**) by using bicyclo[3.1.0]hexan-3-ol in step **B**. LC-MS: m/z 482.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 7.02 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.68 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.51 (s, 1H), 4.20 (s, 2H), 3.99 - 3.95 (m, 1H), 3.82 - 3.76 (m, 10H), 2.28 - 2.21 (m, 2H), 2.07 (s, 3H), 2.00 - 1.94 (m, 2H), 1.85 - 1.82 (m, 2H), 1.23 - 1.21 (m, 2H), 0.49 - 0.46 (m, 1H), 0.38 - 0.37 (m, 1H).

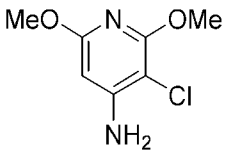
Example A19

4-((4-(3-chloro-2,6-dimethoxypyridin-4-yl)-3-((cyclopentyloxy)methyl)phenyl)amino) tetrahydro-2H-pyran-4-carboxylic acid (Compound 207)



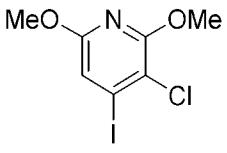


[0427] Step A: 3-chloro-2,6-dimethoxypyridin-4-amine



[0428] To the mixture of 2,6-dimethoxypyridin-4-amine (1 g, 6.5 mmol) in MeCN (8 mL) was added NCS (866 mg, 6.5 mmol). The reaction mixture was stirred at 10 °C for 3 h. The reaction mixture was quenched with H_2O (10 mL), extracted with ethyl acetate (30 mL x 3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~18% EtOAc/PE gradient at 40 mL/min) to give 3-chloro-2,6-dimethoxy-pyridin-4-amine (1.22 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 4.48 (brs, 2H), 3.96 (s, 3H), 3.84 (s, 3H).

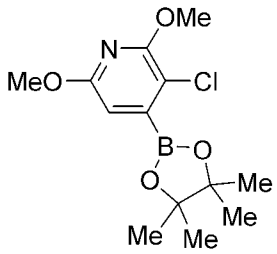
[0429] Step B: 3-chloro-4-iodo-2,6-dimethoxypyridine



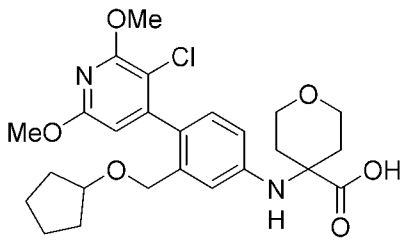
[0430] To the suspension of CuI (2.49 g, 13.1 mmol) in CH_3CN (10 mL) was added tert-butylnitrite (3.37 g, 32.7 mmol, 3.9 mL) at 80 °C under nitrogen. After being stirred for 0.5 h, a solution 3-chloro-2,6-dimethoxy-pyridin-4-amine (1.23 g, 6.5 mmol) in CH_3CN (10 mL) was added dropwise. The resulting

mixture was stirred at 80 °C for 2 h. After cooling, the reaction was quenched with H_2O (20 mL), extracted with ethyl acetate (50 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40g SepaFlash® Silica Flash Column, Eluent of 0~7% EtOAc/PE gradient at 100mL/min) to give 3-chloro-4-iodo-2,6-dimethoxy-pyridine (1.23 g, 62.8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 3.98 (s, 3H), 3.90 (s, 3H).

[0431] Step C: 3-chloro-2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[0432] To the mixture of 3-chloro-4-iodo-2,6-dimethoxy-pyridine (1.23 g, 4.1 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.25 g, 4.9 mmol) in DMF (8 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (335 mg, 411 μmol) and KOAc (1.21 g, 12.3 mmol). The reaction mixture was stirred at 90 °C for 3 h. After cooling, the reaction solution was poured into water (10 mL), extracted with ethyl acetate (25 mL×3). The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to give 3-chloro-2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (300 mg, 24.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 3.99 (s, 3H), 3.89 (s, 3H), 1.34 (s, 12 H).

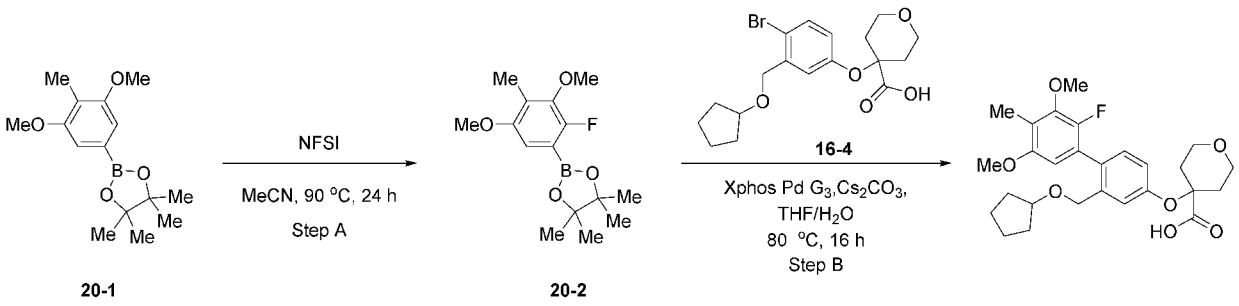


[0433] 4-((4-(3-chloro-2,6-dimethoxypyridin-4-yl)-3-((cyclopentyloxy)methyl)phenyl)amino) tetrahydro-2H-pyran-4-carboxylic acid **(Compound 207)** was synthesized according to the procedures described for the preparation of Example A3 (step **A** and **D**) by using cyclopentanol in step **B** and 3-chloro-2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine in step **D**. LC-MS: m/z 491.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 6.87 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.64

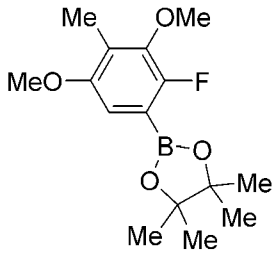
(dd, *J* = 8.4, 2.4 Hz, 1H), 6.25 (s, 1H), 4.17 (dd, *J* = 32.0 Hz, 11.6 Hz, 1H), 4.03 (s, 3H), 3.94 (s, 3H), 3.86 - 3.75 (m, 5H), 2.27 - 2.21 (m, 2H), 2.05 - 2.02 (m, 2H), 1.60 - 1.47 (m, 8H).

Example A20

4-((2-((cyclopentyloxy)methyl)-2'-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)tetrahydro-2H-pyran-4-carboxylic acid (Compound 209)

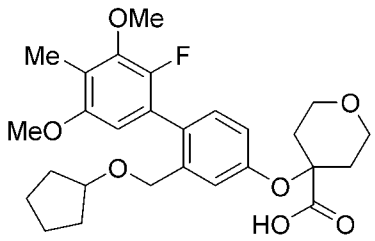


[0434] Step A: 2-(2-fluoro-3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0435] To a solution of 2-(3,5-dimethoxy-4-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.2 g, 43.9 mmol) in THF (100 mL) was added NFSI (20.8 g, 65.8 mmol). The resulting mixture was stirred at 90 °C for 12 h. Then additional NFSI (20.8 g, 65.8 mmol) was added and stirred at 90 °C for another 12 h. After cooling, the solvent was removed under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~4% EtOAc/PE gradient at 100 mL/min) to give 2-(2-fluoro-3,5-dimethoxy-4-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.7 g, 36.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.16 (s, 3H), 1.37 (s, 12H).

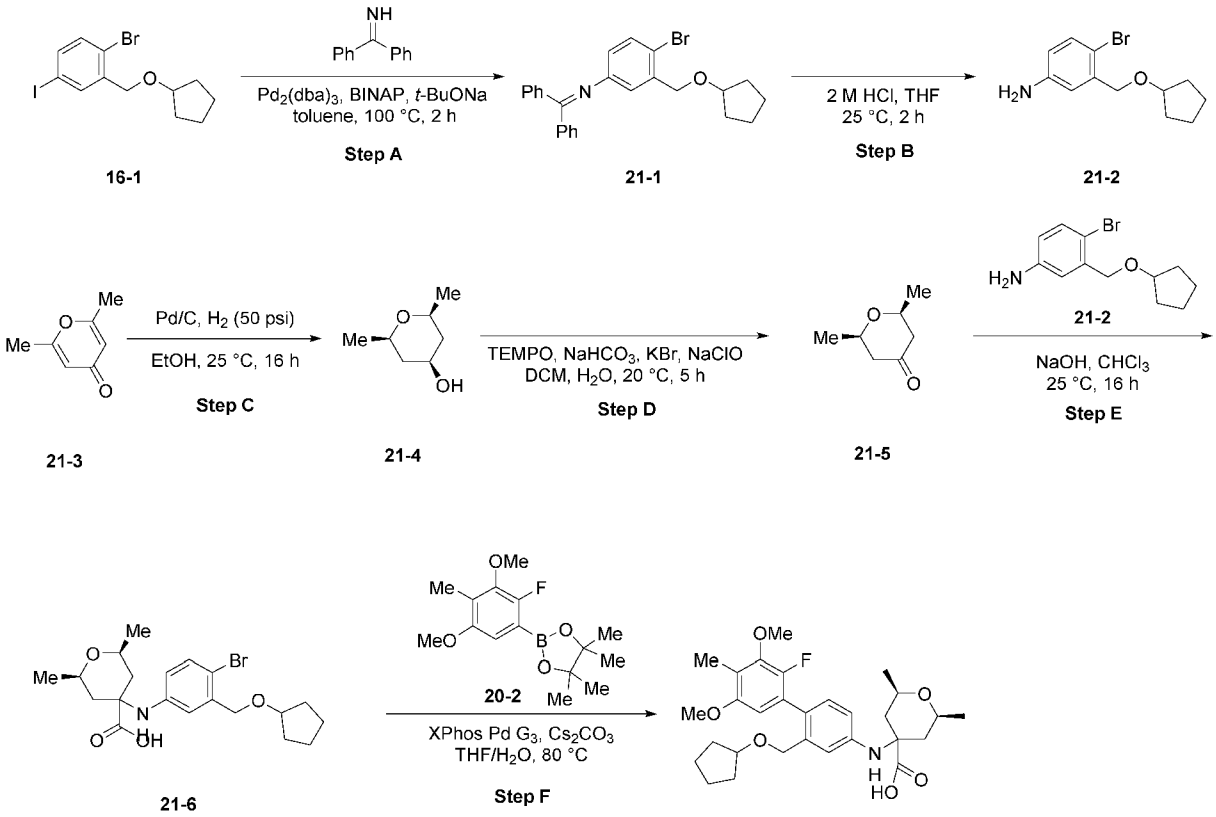
[0436] Step B: 4-((2-((cyclopentyloxy)methyl)-2'-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)oxy)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 209)**



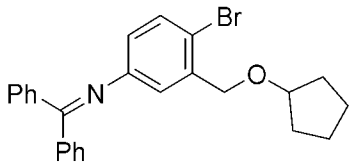
[0437] To the mixture of 4-[4-bromo-3-(cyclopentoxymethyl)phenoxy]tetrahydropyran-4-carboxylic acid (70 mg, 175 μmol) and 2-(2-fluoro-3,5-dimethoxy-4-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (130 mg, 438 μmol) in THF (2 mL) and H_2O (2 mL) were added XPhos Pd G3 (14.8 mg, 17.5 μmol) and Cs_2CO_3 (114 mg, 351 μmol). The reaction mixture was stirred at 80 °C under nitrogen for 16 h. After cooling, the reaction mixture was acidified by 1N HCl to *p*H = 3. The mixture was extracted with ethyl acetate (10 mL x 3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 4g SepaFlash® Silica Flash Column, Eluent of 0~36% EtOAc/PE gradient at 40 mL/min) and further purified by *prep.* HPLC (column: Welch Xtimate C18 150*25 mm*5 μm; mobile phase: [water (0.05% $NH_3 \cdot H_2O$+10 mM NH_4HCO_3)-CH_3CN]; B%: 35% - 65%, 7 min) to give 4-[3-(cyclopentoxymethyl)-4-(2-fluoro-3,5-dimethoxy-4-methyl-phenyl)phenoxy]tetrahydropyran-4-carboxylic acid (21.3 mg, 24.9% yield). LC-MS: m/z 506.3 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.15-7.09 (m, 2H), 6.96 (dd, J = 8.4, 2.6 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.28 (s, 2H), 3.89 - 3.79 (m, 11H), 2.26 -2.20 (m, 2H), 2.18 - 2.10 (m, 5H), 1.67-1.47 (m, 8H).

Example A21

(2R, 6S)-4-((3',5'-dimethoxy-4'-methyl-2-(2-(tetrahydrofuran-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 225)



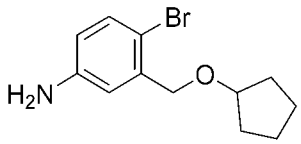
[0438] Step A: N-[4-bromo-3-(cyclopentoxymethyl)phenyl]-1,1-diphenyl-methanimine



[0439] To a solution of 1-bromo-2-(cyclopentoxymethyl)-4-iodo-benzene (600 mg, 1.57 mmol) and diphenylmethanimine (285 mg, 1.57 mmol) in toluene (10 mL) was added $Pd_2(dba)_3$ (72.1 mg, 78.7 μmol), *t*-BuONa (303 mg, 3.15 mmol) and [1-(2-diphenylphosphanyl-1-naphthyl)-2-naphthyl]-diphenyl-phosphane (BINAP) (98.1 mg, 157 μmol). The mixture was stirred at 100 °C for 2 h. After cooling, the mixture was diluted with water (40 mL), extracted with ethyl acetate (25 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of

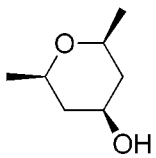
0~2% EtOAc/PE gradient at 40 mL/min) to give N-[4-bromo-3-(cyclopentoxymethyl)phenyl]-1,1-diphenyl-methanimine (653 mg, 95.5% yield). LC-MS: m/z 434.2 $(M+H)^+$.

[0440] Step B: 4-bromo-3-((cyclopentyloxy)methyl)aniline



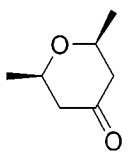
[0441] To a solution of N-[4-bromo-3-(cyclopentoxymethyl)phenyl]-1,1-diphenyl-methanimine (653 mg, 1.50 mmol) in THF (10 mL) was added 2 M HCl (752 μL). The reaction mixture was stirred at 25 °C for 2 h. The mixture was diluted with water (40 mL), basified by *sat. aq.* $NaHCO_3$ (20 mL), extracted with ethyl acetate (25 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% EtOAc/PE gradient at 40 mL/min) to give 4-bromo-3-(cyclopentoxymethyl)aniline (323 mg, 79.5% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 6.39 (dd, J = 8.4, 3.2 Hz, 1H), 4.32 (s, 2H), 4.06 - 3.89 (m, 1H), 3.61 (s, 2H), 1.80 - 1.36 (m, 8H).

[0442] Step C: (2R,4S,6S)-2,6-dimethyltetrahydro-2H-pyran-4-ol



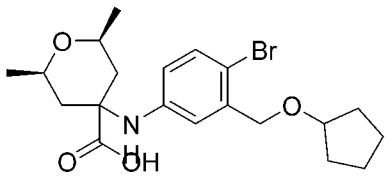
[0443] To a solution of 2,6-dimethyl-4H-pyran-4-one (10.0 g, 80.6 mmol) in EtOH (150 mL) was added 10% Pd/C (4 g) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (45 Psi) at 25 °C for 16 h. The suspension was filtered through a pad of Celite® and the pad was washed with ethanol (50 mL). The filtrate was concentrated to dryness under reduced pressure to give crude (2R,4S,6S)-2,6-dimethyltetrahydro-2H-pyran-4-ol (10 g), which used in the next step without further purification.

[0444] Step D: (2R, 6S)-2,6-dimethyldihydro-2H-pyran-4(3H)-one



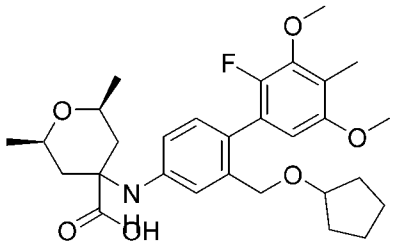
[0445] To a solution of (2R,4S,6S)-2,6-dimethyltetrahydro-2H-pyran-4-ol (10.0 g, 76.8 mmol, crude) in DCM (120 mL) was added a solution of $NaHCO_3$ (645 mg, 7.68 mmol) and KBr (914 mg, 7.68 mmol) in H_2O (40 mL). Then TEMPO (121 mg, 768 μmol) was added. The mixture was treated at 0 °C under vigorous stirring with *aq.* NaClO (78.6 g, 84.5 mmol, 5%~7%) over 1 h. Then the whole system was allowed to stir at 20 °C for 5 h. The reaction mixture was poured into H_2O (100 mL), extracted with dichloromethane (100 mL x 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure to give crude (2,6-dimethyldihydro-2H-pyran-4(3H)-one (7 g, crude), which used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 - 3.72 (m, 2H), 2.39 - 2.32 (m, 2H), 2.27 - 2.17 (m, 2H), 1.34 (d, J = 6.2 Hz, 6H)

[0446] Step E (2R,6S)-4-((4-bromo-3-((cyclopentyloxy)methyl)phenyl)amino)-2,6-dimethyltetrahydro-2H-pyran-4-carboxylic acid



[0447] To a solution of 4-bromo-3-((cyclopentyloxy)methyl)aniline (500 mg, 1.85 mmol) and (2R,6S)-2,6-dimethyltetrahydro-4H-pyran-4-one (474 mg, 3.70 mmol, crude) in THF (4 mL) was added NaOH (370 mg, 9.25 mmol) and $CHCl_3$ (1.10 g, 9.25 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 16 h. Then the mixture was poured into *sat. aq.* NH_4Cl (150 mL) at 0 °C, extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/PE gradient at 10 mL/min) to give (2R,6S)-4-((4-bromo-3-((cyclopentyloxy)methyl)phenyl)amino)-2,6-dimethyltetrahydro-2H-pyran-4-carboxylic acid (320 mg, crude). LC-MS: m/z 426.2 $(M+H)^+$.

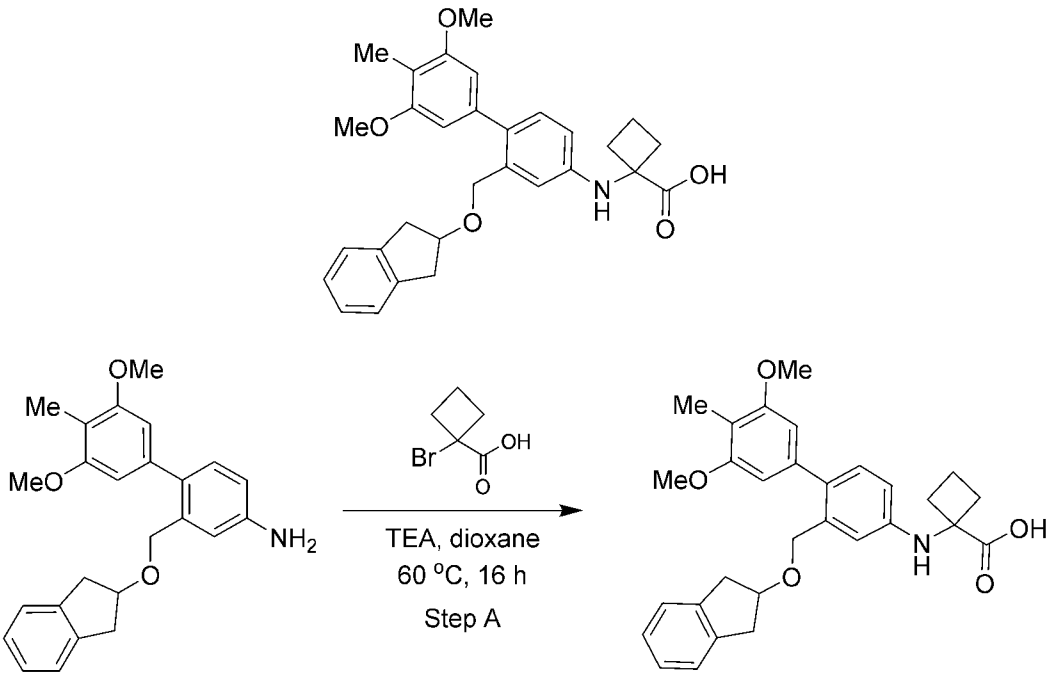
[0448] Step F (2R,6S)-4-((2-((cyclopentyloxy)methyl)-2'-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)-2,6-dimethyltetrahydro-2H-pyran-4-carboxylic acid **(Compound 225)**



[0449] The mixture of (2R,6S)-4-((4-bromo-3-((cyclopentyloxy)methyl)phenyl)amino)-2,6-dimethyltetrahydro-2H-pyran-4-carboxylic acid (320 mg, 751 μmol, crude), 2-(2-fluoro-3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (667 mg, 1.13 mmol, 50% purity), XPhos Pd G3 (63.5 mg, 75.1 μmol), Cs_2CO_3 (489 mg, 1.50 mmol) in THF (5 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times. The resulting mixture was stirred at 110 °C for 16 h under N_2 atmosphere. After cooling, the reaction mixture was filtered and the filtrate was evaporated to give a residue. The crude product was purified by *prep.* HPLC (Column: Boston Prime C18 150*30mm*5μm Eluent: 30% to 60% water (0.05% $NH_3 \cdot H_2O$+10 mM NH_4HCO_3)-CH_3CN) to give the product (2R,6S)-4-((2-((cyclopentyloxy)methyl)-2'-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)-2,6-dimethyltetrahydro-2H-pyran-4-carboxylic acid (52.4 mg, 13.5% yield. LC-MS: m/z 516.4 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d6*) δ 6.88 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 5.2 Hz, 1H), 4.11 (s, 2H), 3.84 - 3.60 (m, 9H), 2.43 - 2.34 (m, 2H), 2.08 (s, 3H), 1.60 - 1.36 (m, 8H), 1.23 - 1.13 (m, 2H), 1.09 (d, J = 5.6 Hz, 6H).

Example A22

1-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)cyclobutane-1-carboxylic acid (Compound 110)

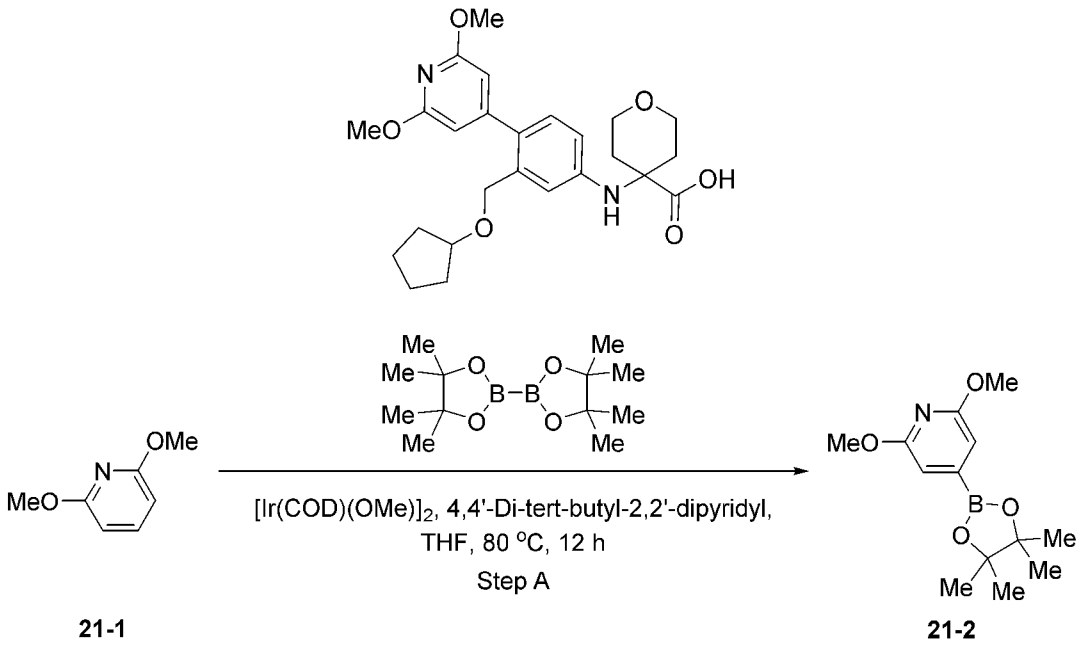


2-5 **Compound 110**

[0450] To a mixture of 2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-amine (70 mg, 0.18 mmol) in dioxane (2 mL) was added TEA (0.15 mL, 1.08 mmol). Then the mixture was heated to 60 °C, and 1-bromocyclobutane-1-carboxylic acid (49 mg, 0.27 mmol) in dioxane (1 mL) was added. The resulting mixture was stirred at 60 °C overnight under N_2 protection. After cooling, the reaction mixture was concentrated. The crude was purified by *prep*. HPLC (0.1% NH_4HCO_3 in water and acetonitrile) to afford 1-((2-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)cyclobutane-1-carboxylic acid (29 mg, 34% yield). LC-MS: m/z 488.2 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.21 - 7.17 (m, 2H), 7.13 - 7.11 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.53 (s, 2H), 6.31 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.38 - 4.33 (m, 1H), 4.32 (s, 2H), 3.72 (s, 6H), 3.08 (dd, *J* = 16.0, 6.4 Hz, 2H), 2.85 (d, *J* = 16.0, 3.6 Hz, 2H), 2.61 - 2.53 (m, 2H), 2.17 - 2.07 (m, 2H), 2.00 (s, 3H), 1.97 - 1.87 (m, 2H).

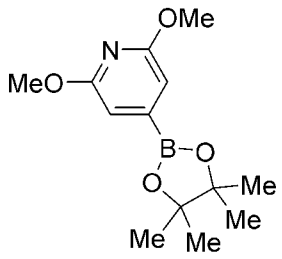
Example A23

4-((3-((cyclopentyloxy)methyl)-4-(2,6-dimethoxypyridin-4-yl)phenyl)amino) tetrahydro-2H-pyran-4-carboxylic acid (Compound 152)

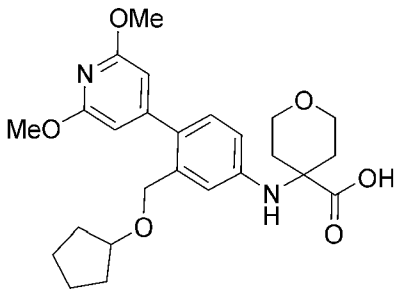


21-1 **21-2**

[0451] Step A 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



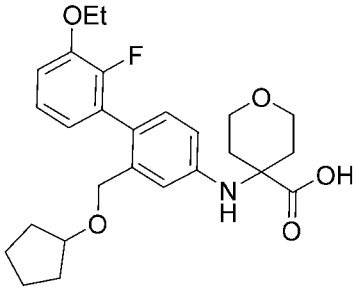
[0452] To a solution of 2,6-dimethoxypyridine (1.0 g, 7.19 mmol) and bis(pinacolato)diboron (912 mg, 3.59 mmol) in THF (15 mL) were added 4,4'-Di-tert-butyl-2,2'-dipyridyl (dtbpy) (96.4 mg, 0.36 mmol) and $[Ir(COD)OMe]_2$ (119.1 mg, 0.18 mmol). The resulting mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. Then it was concentrated. The residue was purified by silica gel column chromatography (0~10% EtOAc in PE) to afford 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (640 mg, 33.6% yield) as a white solid. LC-MS: m/z 266.2 $(M+H)^+$.

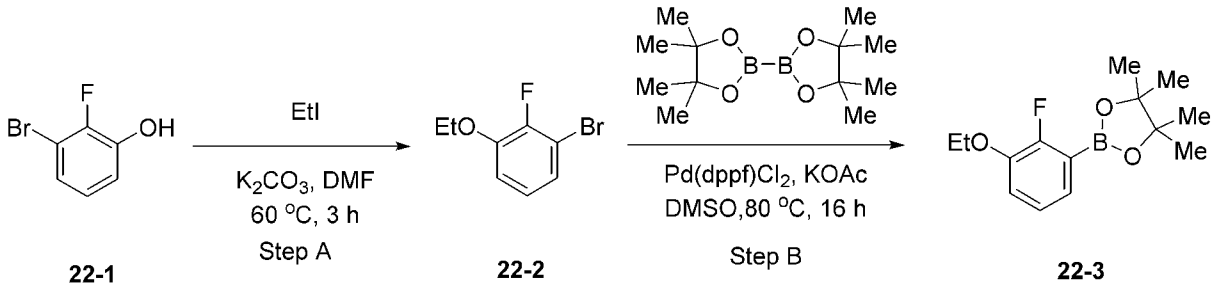


[0453] 4-((3-((cyclopentyloxy)methyl)-4-(2,6-dimethoxypyridin-4-yl)phenyl)amino) tetrahydro-2H-pyran-4-carboxylic acid (**Compound 152**) was synthesized according to the procedures described for the preparation of Example **A3** (step **B** to **D**) by using cyclopentanol in step **B** , 4-aminotetrahydro-2H-pyran-4-carboxylic acid in step **C** and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine in step **D**. LC-MS: m/z 457.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 6.98 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 2.5 Hz, 1H), 6.57 - 6.48 (m, 1H), 6.32 (s, 2H), 4.18 (s, 2H), 3.92 - 3.87 (m, 1H), 3.85 (s, 6H), 3.66 - 3.58 (m, 4H), 2.08 -- 1.94 (m, 2H), 1.84 (d, J = 13.4 Hz, 2H), 1.66 - 1.54 (m, 6H), 1.50 - 1.37 (m, 2H).

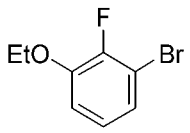
Example A24

4-((2-((cyclopentyloxy)methyl)-3'-ethoxy-2'-fluoro-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 245)



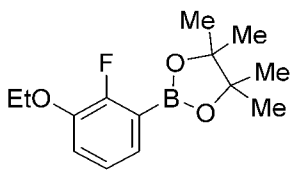


[0454] Step A 1-bromo-3-ethoxy-2-fluorobenzene

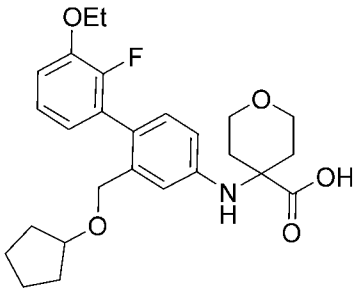


[0455] To a solution of 3-bromo-2-fluorophenol (5.0 g, 26.2 mmol) in DMF (50 mL) was added K_2CO_3 (9.05 g, 65.5 mmol) and iodoethane (3.14 mL, 39.3 mmol). The resulting mixture was stirred at 60 °C for 3 h. After cooling, the mixture was diluted with brine (100 mL), extracted with EtOAc (200 mL x 2). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~15% EtOAc/PE gradient @ 100 mL/min) to give 1-bromo-3-ethoxy-2-fluorobenzene (5.01 g, 87% yield).

[0456] Step B 2-(3-ethoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



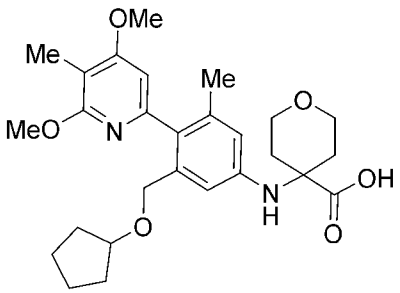
[0457] To a solution of 1-bromo-3-ethoxy-2-fluorobenzene (1.8 g, 8.22 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4.17 g, 16.4 mmol) in DMSO (15 mL) was added KOAc (2.42 g, 24.7 mmol) and $Pd(dppf)Cl_2$ (601 mg, 822 μmol). The reaction mixture was stirred at 100 °C for 2 h. After cooling, the mixture was diluted with brine (100 mL), extracted with EtOAc (100 mL x 2). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (Silica Flash Column, Eluent of 0~3% EtOAc/PE gradient) to give 2-(3-ethoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.05 g, 48% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.19 (s, 1H), 7.03 - 6.92 (m, 2H), 4.05 - 4.00 (m, 2H), 1.34 (t, J = 7.0 Hz, 3H), 1.29 (s, 12H).

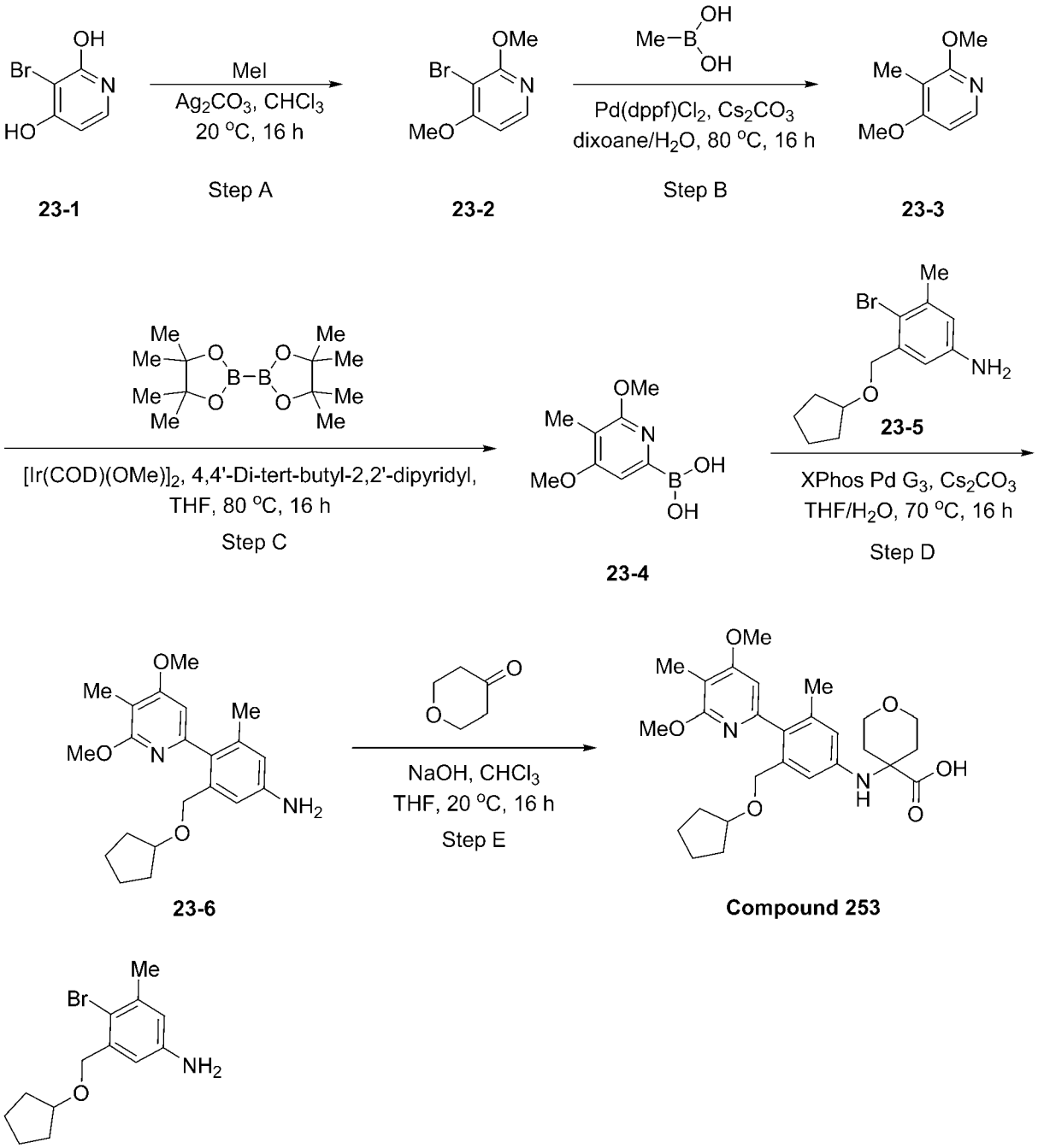


[0458] 4-((2-((cyclopentyloxy)methyl)-3'-ethoxy-2'-fluoro-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (**Compound 245**) was synthesized according to the procedures described for the preparation of Example A3 (step **B** and **D**) by using cyclopentanol in step **B**, 4-aminotetrahydro-2H-pyran-4-carboxylic acid in step **C** and 2-(3-ethoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in step **D**. LC-MS: m/z 458.5 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 - 7.00 (m, 2H), 6.98 - 6.91 (m, 1H), 6.83 (s, 1H), 6.78 (t, J = 7.0 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 4.23 (s, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.93 - 3.73 (m, 5H), 2.42 - 2.23 (m, 2H), 2.01 - 1.82 (m, 2H), 1.64 - 1.40 (m, 11H).

Example A25

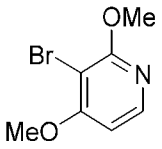
4-((3-((cyclopentyloxy)methyl)-4-(4,6-dimethoxy-5-methylpyridin-2-yl)-5-methylphenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 253)





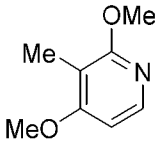
[0459] 4-bromo-3-((cyclopentyloxy)methyl)-5-methylaniline (**23-5**) was synthesized according to the procedures described for the preparation of intermediate **21-2**. LC-MS: m/z 284.1 $(M+H)^+$.

[0460] Step A 3-bromo-2,4-dimethoxypyridine



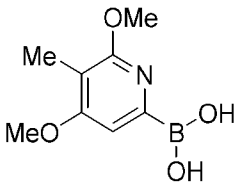
[0461] To a solution of 3-bromopyridine-2,4-diol (9.0 g, 47.4 mmol) in $CHCl_3$ (100 mL) was added iodomethane (14.7 mL, 237 mmol) and Ag_2CO_3 (52.3 g, 189 mmol). The mixture was stirred at 20 °C for 16 h. After filtration, the filtrate was concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/PE gradient @ 100 mL/min) to afford 3-bromo-2,4-dimethoxy-pyridine (7.2 g, 69.7% yield). LC-MS: m/z 219.9 $(M+H)^+$.

[0462] Step B 2,4-dimethoxy-3-methylpyridine



[0463] To a solution of 3-bromo-2,4-dimethoxy-pyridine (8.0 g, 36.7 mmol) and methylboronic acid (6.59 g, 110 mmol) in dioxane (100 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (2.68 g, 3.30 mmol) and Cs_2CO_3 (23.9 g, 73.4 mmol). The mixture was stirred at 80 °C for 12 h under nitrogen. After cooling, the reaction was diluted with H_2O (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (10/1 to 3/1 EtOAc/PE) to afford 2,4-dimethoxy-3-methyl-pyridine (3.6 g, 64.1% yield). LC-MS: m/z 155.1 $(M+H)^+$.

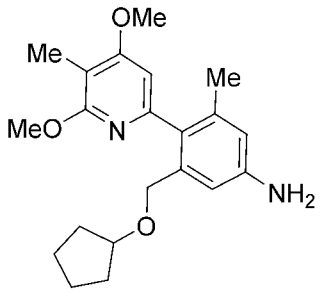
[0464] Step C (4,6-dimethoxy-5-methylpyridin-2-yl)boronic acid



[0465] To a solution of 2,4-dimethoxy-3-methyl-pyridine (100 mg, 653 μmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (166 mg, 653 μmol) in THF (1 mL) was added $[Ir(COD)OMe]_2$ (4.33 mg, 6.53 μmol) and 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (dtbpy) (3.50 mg, 13.1 μmol). The mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried

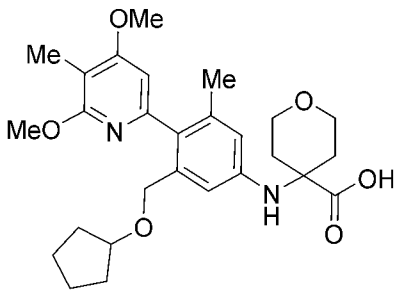
over Na_2SO_4, filtered and concentrated to afford (4,6-dimethoxy-5-methyl-2-pyridyl)boronic acid (120 mg, crude), which was used in the next step without further purification. LC-MS: m/z 198.7 $(M+H)^+$.

[0466] Step D (4,6-dimethoxy-5-methylpyridin-2-yl)boronic acid



[0467] To a solution of (4,6-dimethoxy-5-methyl-2-pyridyl)boronic acid (120 mg, 609 μmol) and 4-bromo-3-((cyclopentyloxy)methyl)-5-methylaniline (86.6 mg, 305 μmol) in THF (1 mL) and H_2O (1 mL) was added XPhos Pd G3 (25.8 mg, 30.5 μmol) and Cs_2CO_3 (198 mg, 609 μmol). The mixture was stirred at 70 °C for 16 h under nitrogen. After cooling, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/PE gradient @ 18 mL/min) to afford 3-((cyclopentyloxy)methyl)-4-(4,6-dimethoxy-5-methylpyridin-2-yl)-5-methylaniline (50 mg, 46.1% yield). LC-MS: m/z 379.0 $(M+Na)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.51 (s, 1H), 6.47 (s, 1H), 4.18 (s, 2H), 3.90 (s, 3H), 3.89 -3.81 (m, 4H), 3.66 (s, 2H), 2.06 (s, 3H), 1.91 (s, 3H), 1.63 - 1.45 (m, 8H).

[0468] Step E 4-((3-((cyclopentyloxy)methyl)-4-(4,6-dimethoxy-5-methylpyridin-2-yl)-5-methylphenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 253)**

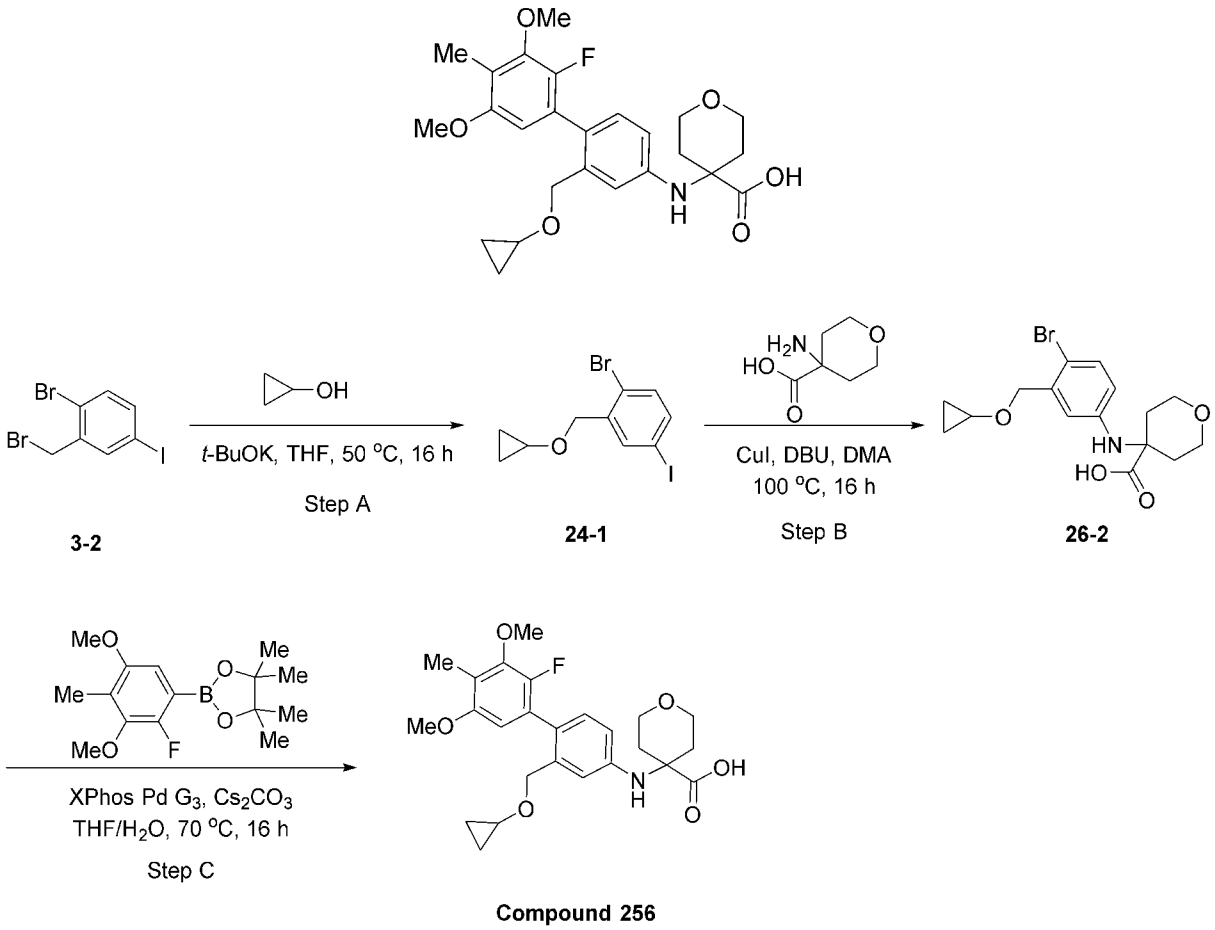


[0469] To a solution of 3-(cyclopentoxymethyl)-4-(4,6-dimethoxy-5-methyl-2-pyridyl)-5-methyl-aniline (50 mg, 140 μmol) and tetrahydropyran-4-one (21.1 mg, 210 μmol) in THF (1 mL) was added NaOH (28.1 mg, 701 μmol) and chloroform (83.7 mg, 701 μmol). The mixture was stirred at 20 °C for 16

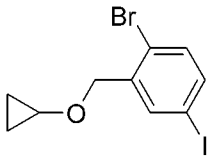
h. The reaction mixture was quenched by addition 1 N HCl to *p*H=7, extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by *prep*. HPLC (Column: Welch Xtimate C18; Mobile Phase A: water (0.1% NH_3H_2O+NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 25 mL/min; Gradient: 25% B 5 min 25% B to 55% B in 20 min) to afford 4-((3-((cyclopentyloxy)methyl)-4-(4,6-dimethoxy-5-methylpyridin-2-yl)-5-methylphenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (8.44 mg, 12.0% yield). LC-MS: m/z 485.3 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.65 (s, 1H), 6.56 (s, 1H), 6.54 (s, 1H), 4.15 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 - 3.73 (m, 5H), 2.25 - 2.17 (m, 2H), 2.05 (s, 3H), 2.03 - 1.99 (m, 5H), 1.60 - 1.45 (m, 8H).

Example A26

4-((2-(cyclopropoxymethyl)-2'-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 256)

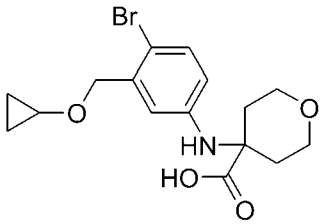


[0470] Step A 1-bromo-2-(cyclopropoxymethyl)-4-iodobenzene



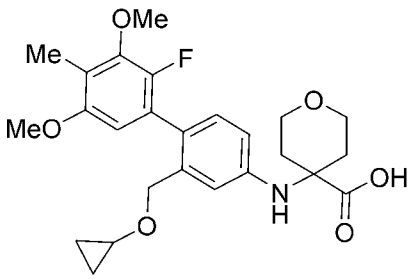
[0471] To a solution of 1-bromo-2-(bromomethyl)-4-iodobenzene (2.0 g, 5.32 mmol) in THF (20 mL) was added *t*-BuOK (717 mg, 6.38 mmol) and cyclopropanol (580 uL, 6.38 mmol). The reaction mixture was stirred at 50 °C for 16 h. after cooling, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/PE gradient @ 100 mL/min) to afford 1-bromo-2-(cyclopropoxymethyl)-4-iodo-benzene (1.4 g, 74.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 1.2 Hz, 1H), 7.48 (dd, J = 8.4, 0.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 4.58 (s, 2H), 3.48 - 3.43 (m, 1H), 0.74 - 0.70 (m, 2H), 0.59 - 0.56 (m, 2H).

[0472] Step B 4-((4-bromo-3-(cyclopropoxymethyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid



[0473] To a solution of 1-bromo-2-(cyclopropoxymethyl)-4-iodo-benzene (700 mg, 1.98 mmol) and 4-aminotetrahydro-2H-pyran-4-carboxylic acid (432 mg, 2.97 mmol) in DMA (15 mL) was added CuI (75.5 mg, 397 μmol) and DBU (604 mg, 3.97 mmol). The mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~6% MeOH/DCM gradient @ 80 mL/min) to afford 4-((4-bromo-3-(cyclopropoxymethyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (330 mg, 45.0% yield). LC-MS: m/z 370.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 3.0 Hz, 1H), 6.48 (dd, J = 8.8, 3.0 Hz, 1H), 4.50 (s, 2H), 3.81 - 3.70 (m, 4H), 3.43 - 3.41 (m, 1H), 2.22 - 2.15 (m, 2H), 2.15 - 1.95 (m, 2H), 0.64 - 0.60 (m, 2H), 0.53 - 0.49 (m, 2H).

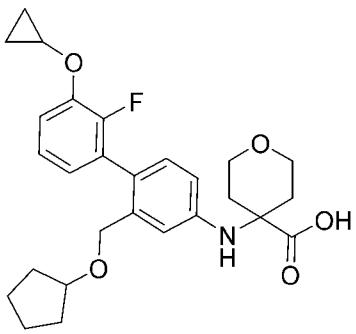
[0474] Step C 4-((2-(cyclopropoxymethyl)-2'-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 256)**

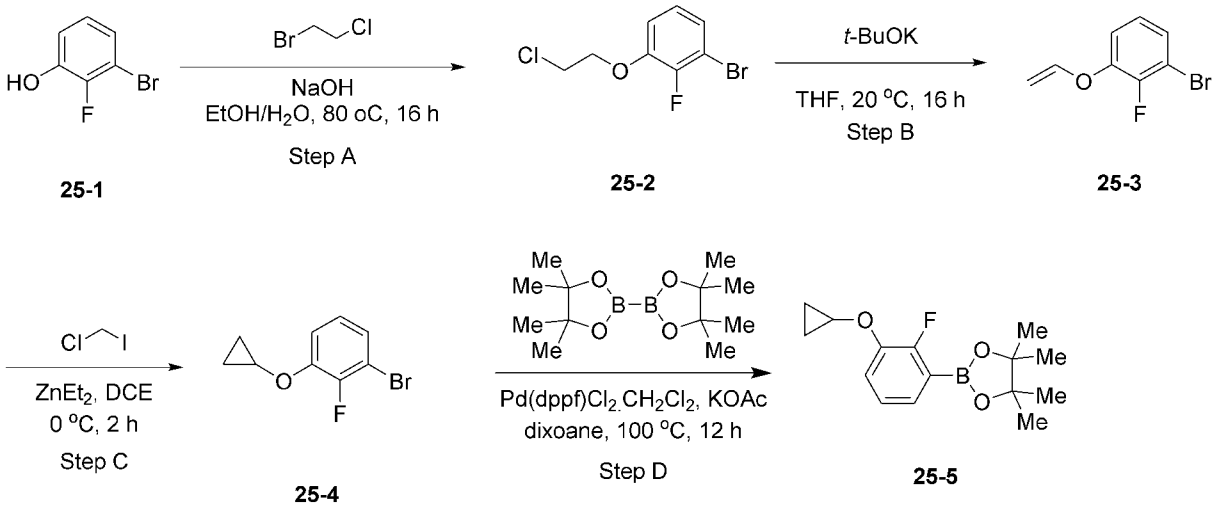


[0475] To a solution of 4-[4-bromo-3-(cyclopropoxymethyl)anilino]tetrahydropyran-4-carboxylic acid (150 mg, 405 μmol) and 2-(2-fluoro-3,5-dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (180 mg, 608 μmol) in THF (2 mL) and H_2O (2 mL) was added XPhos Pd G3 (34.3 mg, 40.5 μmol) and Cs_2CO_3 (264 mg, 810 μmol). The mixture was stirred at 70 °C for 16 h under nitrogen. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated. The residue was purified by *prep*. HPLC (Column: Welch Xtimate C18; Mobile Phase A: water (0.1% NH_3H_2O+NH_4HCO_3), Mobile Phase B: CAN; Flow rate: 25 mL/min; Gradient: 35% B 5 min 35% B to 65% B in 20 min) to afford 4-((2-(cyclopropoxymethyl)-2'-fluoro-3',5'-dimethoxy-4'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (81.59 mg, 43.4% yield). Alternatively, $Pd(dppf)Cl_2$ and and Na_2CO_3 can be used in place of XPhos Pd G3 and Cs_2CO_3. LC-MS: m/z 460.3 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.96 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.66 (dd, J = 8.4, 2.4 Hz, 1H), 6.48 (d, J = 5.6 Hz, 1H), 4.30 (s, 2H), 3.84 (s, 3H), 3.82 - 3.73 (m, 7H), 3.31 - 3.23 (m, 1H), 2.26 - 2.22 (m, 2H), 2.20 (s, 3H), 2.14 - 1.97 (m, 2H), 0.37 - 0.36 (m, 4H).

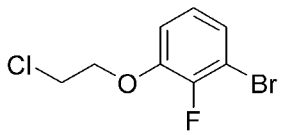
Example A27

4-((2-((cyclopentyloxy)methyl)-3'-cyclopropoxy-2'-fluoro-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 265)



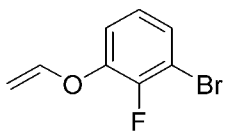


[0476] Step A 1-bromo-3-(2-chloroethoxy)-2-fluorobenzene



[0477] To a solution of 3-bromo-2-fluoro-phenol (5.0 g, 26.2 mmol) in EtOH (50 mL) was added NaOH (1.05 g, 26.2 mmol) in H_2O (10 mL). After being stirred for 0.5 h, to the mixture was added 1-bromo-2-chloro-ethane (4.34 mL, 52.4 mmol). The resulting reaction mixture was stirred at 80 °C for 16 h. After cooling, the reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0-10% EtOAc/PE gradient @ 100 mL/min) to give 1-bromo-3-(2-chloroethoxy)-2-fluorobenzene (4.6 g, 69.3% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 - 7.05 (m, 1H), 6.89 - 6.87 (m, 2H), 4.23 (d, J = 5.2 Hz, 2H), 3.76 (d, J = 5.2 Hz, 2H).

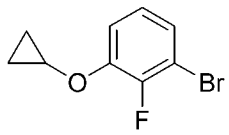
[0478] Step B 1-bromo-2-fluoro-3-(vinyloxy)benzene



[0479] To a solution of 1-bromo-3-(2-chloroethoxy)-2-fluoro-benzene (4.6 g, 18.2 mmol) in THF (40 mL) was added *t*-BuOK (4.07 g, 36.3 mmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched by water (50 mL), extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by

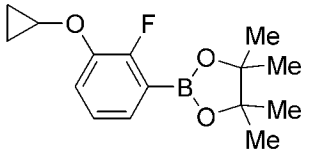
flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0-5% EtOAc/PE gradient @100 mL/min) to give 1-bromo-2-fluoro-3-vinyloxy-benzene (2.8 g, 71.1% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 - 7.19 (m, 1H), 6.96 - 6.90 (m, 2H), 6.54 (dd, J = 14.0, 6.4 Hz, 1H), 4.68 (dd, J = 13.6, 2.4 Hz, 1H), 4.43 (dd, J = 6.4, 2.4 Hz, 1H).

[0480] Step C 1-bromo-3-cyclopropoxy-2-fluorobenzene

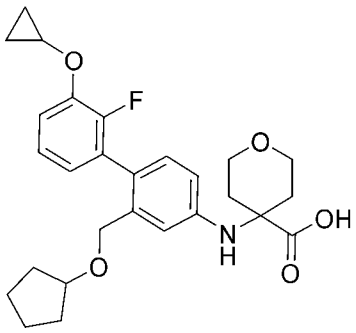


[0481] To a solution of 1-bromo-2-fluoro-3-vinyloxy-benzene (1.0 g, 4.61 mmol) and chloroiodomethane (1.34 mL, 18.4 mmol) in DCE (15 mL) was added 2 M $ZnEt_2$ (5.76 mL, 11.52 mmol). The reaction mixture was stirred at 0 °C for 2 h. Then it was quenched with *sat. aq.* NH_4Cl (10 mL), extracted with DCM (15 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0-2% EtOAc/PE gradient @ 40 mL/min) to give 1-bromo-3-(cyclopropoxy)-2-fluoro-benzene (0.9 g, 84.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 - 7.13(m, 1H), 7.08 - 7.03 (m, 1H), 6.92 -6.85 (m, 1H), 3.78 - 3.72 (m, 1H), 0.80 - 0.72 (m, 4H)

[0482] Step D 2-(3-cyclopropoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



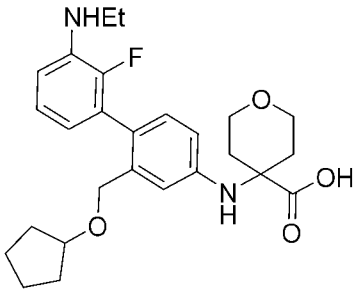
[0483] To a solution of 1-bromo-3-(cyclopropoxy)-2-fluoro-benzene (0.9 g, 3.90 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.98 g, 7.79 mmol) in dioxane (20 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (318 mg, 390 μmol) and KOAc (1.15 g, 11.7 mmol). The mixture was stirred at 100 °C for 12 h. After cooling, the reaction mixture was quenched by water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~3% EtOAc/PE gradient @ 80 mL/min) to give 2-(3-cyclopropoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.6 g, 55.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.26 (m, 1H), 7.20 (s, 1H), 6.99 (t, J = 7.6 Hz, 1H), 3.78 - 3.73 (m, 1H), 1.29 (s, 12H), 0.75 - 0.68 (m, 4H).

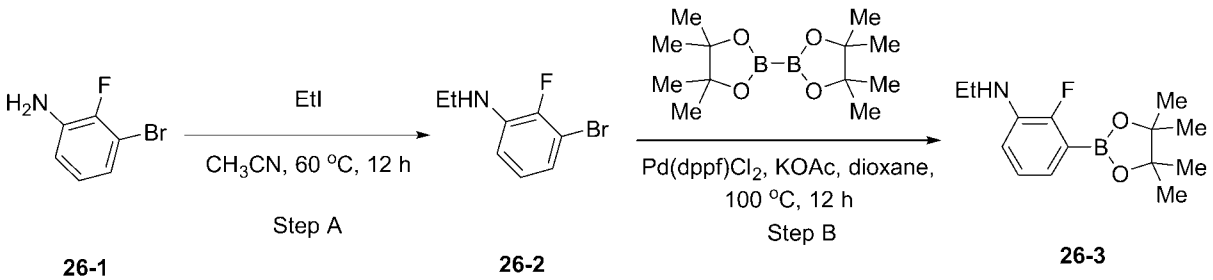


[0484] 4-((2-((cyclopentyloxy)methyl)-3'-cyclopropoxy-2'-fluoro-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 265)** was synthesized according to the procedures described for the preparation of Example A3 (step **A** and **D**) by using cyclopentanol in step **B** and 2-(3-cyclopropoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in step **D**. LC-MS: m/z 470.3 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.34 (s, 1H), 7.11 (s, 1H), 7.00 - 6.91 (m, 1H), 6.87 - 6.77 (m, 2H), 6.65 (s, 1H), 4.21 (s, 2H), 3.94 - 3.74 (m, 6H), 2.33 - 2.15 (m, 2H), 2.12 - 1.96 (m, 2H), 1.64 - 1.43 (m, 8H), 0.90 - 0.72 (m, 4H).

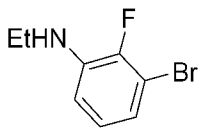
Example A28

4-((2-((cyclopentyloxy)methyl)-3'-(ethylamino)-2'-fluoro-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 278)



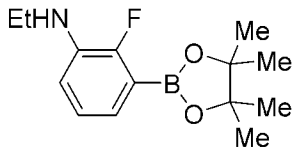


[0485] Step A 3-bromo-N-ethyl-2-fluoroaniline

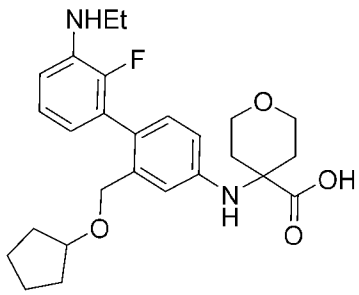


[0486] To a solution of 3-bromo-2-fluoroaniline (1.0 g, 5.26 mmol) in DMF (5 mL) was added iodoethane (337 uL, 4.21 mmol). The mixture was stirred at 60 °C for 12 h. The reaction mixture was quenched by water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0-10% EtOAc/PE gradient @ 40 mL/min) to give 3-bromo-N-ethyl-2-fluoro-aniline (0.5 g, 43.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 - 6.83 (m, 1H), 6.81 - 6.78 (m, 1H), 6.63 - 6.59 (m, 1H), 3.89 (s, 1H), 3.25 - 3.16 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H).

[0487] Step B N-ethyl-2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



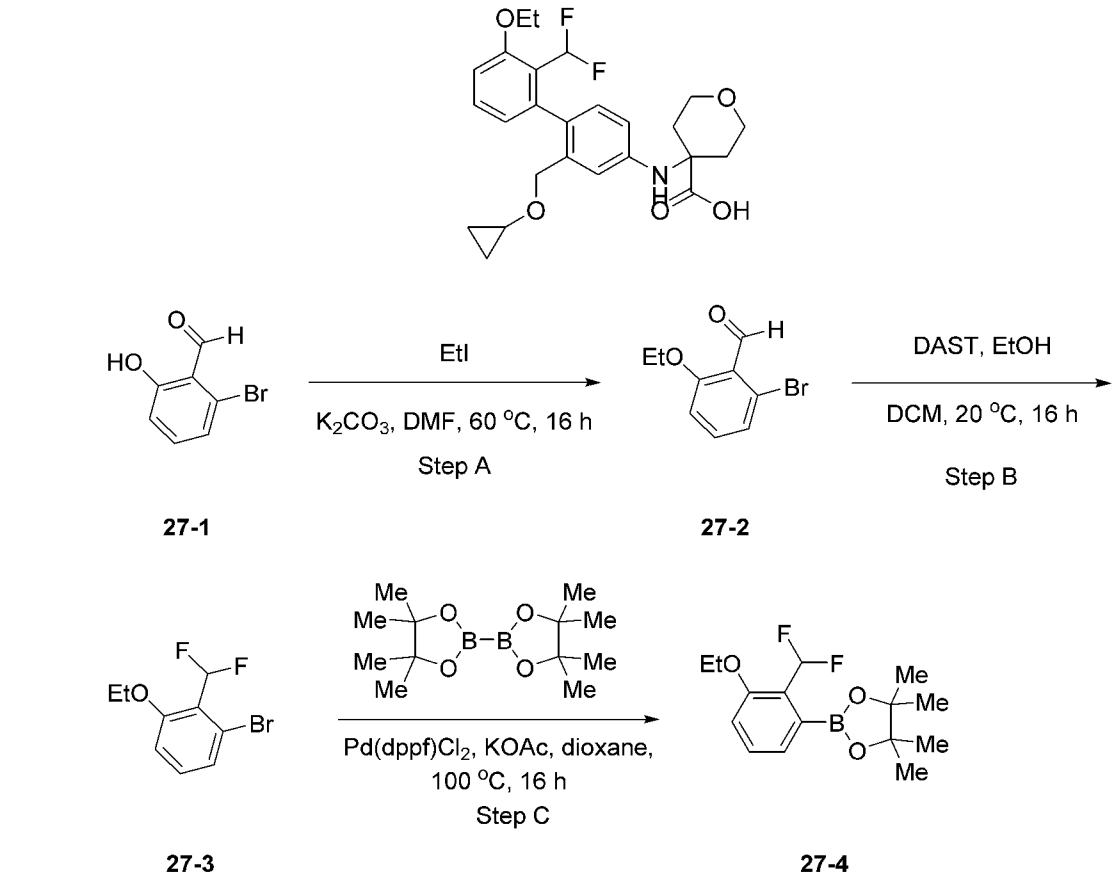
[0488] To a solution of 3-bromo-N-ethyl-2-fluoro-aniline (0.5 g, 2.29 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.05 g, 4.13 mmol) in dioxane (10 mL) was added $Pd(dppf)Cl_2$ (168 mg, 229 μmol) and KOAc (675 mg, 6.88 mmol). The mixture was stirred at 100 °C for 12 h. The reaction mixture was quenched by water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/PE gradient @ 40 mL/min) to give N-ethyl-2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.52 g, 85.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 - 6.96 (m, 2H), 6.83 - 6.76 (m, 1H), 3.82 (brs, 1H), 3.23 - 3.14 (m, 2H), 1.36 (s, 12H), 1.30 (t, J = 7.2 Hz, 3H).



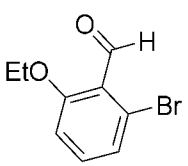
[0489] 4-((2-((cyclopentyloxy)methyl)-3'-(ethylamino)-2'-fluoro-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 278)** was synthesized according to the procedures described for the preparation of Example A3 (step **A** and **D**) by using cyclopentanol in step **B** and N-ethyl-2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline in step **D**. LC-MS: m/z 457.3 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.00 - 6.92 (m, 2H), 6.86 (d, J = 2.4 Hz, 1H), 6.76 - 6.65 (m, 2H), 6.48 (t, J = 6.4 Hz, 1H), 4.24 (s, 2H), 3.88 - 3.74 (m, 5H), 3.18-3.26 (q, J = 7.2 Hz, 1H), 2.30 - 2.20 (m, 2H), 2.06 - 1.96 (m, 2H), 1.64 - 1.43 (m, 8H), 1.28 (t, J = 7.2 Hz, 3H).

Example A29

4-((2-(cyclopropoxymethyl)-2'-(difluoromethyl)-3'-ethoxy-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 279)

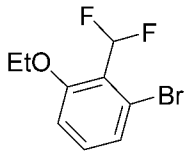


[0490] Step A 2-bromo-6-ethoxybenzaldehyde



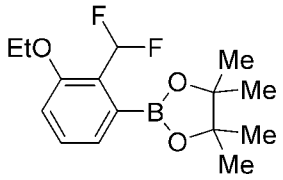
[0491] To a solution of 2-bromo-6-hydroxybenzaldehyde (5.0 g, 24.9 mmol) in DMF (50 mL) was added iodoethane (2.98 mL, 37.3 mmol) and K_2CO_3 (6.88 g, 49.8 mmol). The reaction mixture was stirred at 60 °C for 16 h. After cooling, the mixture was diluted with H_2O (100 mL), extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (50 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/PE gradient @ 50 mL/min) to afford 2-bromo-6-ethoxybenzaldehyde (5.0 g, 87.8% yield). LC-MS: m/z 228.9 $(M+H)^+$.

[0492] Step B 1-bromo-2-(difluoromethyl)-3-ethoxybenzene



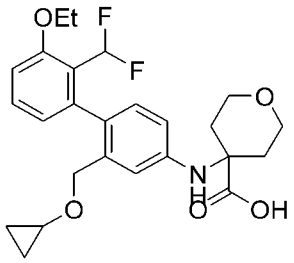
[0493] To a solution of 2-bromo-6-ethoxybenzaldehyde (2.0 g, 8.73 mmol) in DCM (20 mL) was added DAST (1.73 mL, 13.1 mmol) and EtOH (402 mg, 8.73 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 16 h. The mixture was diluted with H_2O (20 mL), extracted with DCM (10 mL x 2). The combined organic phases were washed with brine (20 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~7% EtOAc/PE gradient @ 50 mL/min) to give 1-bromo-2-(difluoromethyl)-3-ethoxybenzene (1.1 g, 4.38 mmol, 50.2% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.05 (m, 3H), 6.88 (d, J = 7.2 Hz, 1H), 4.10 (q, J = 6.8 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H).

[0494] Step C 2-(2-(difluoromethyl)-3-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0495] To a solution of 1-bromo-2-(difluoromethyl)-3-ethoxybenzene (1.0 g, 3.98 mmol) in DMSO (10 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.52 g, 5.97 mmol), $Pd(dppf)Cl_2$ (145.72 mg, 199 μmol) and KOAc (1.17 g, 12.0 mmol). The reaction mixture was stirred at 100 °C for 16 h under nitrogen. After cooling, the mixture was diluted with water (100 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4 and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~7% EtOAc/PE gradient @

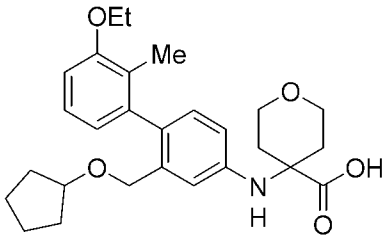
30 mL/min) to give 2-(2-(difluoromethyl)-3-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (900 mg, 75.8% yield). LC-MS: m/z 299.2 $(M+H)^+$.

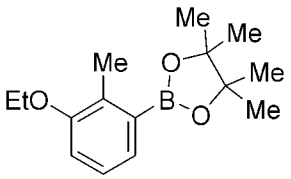


[0496] 4-((2-(cyclopropoxymethyl)-2'-(difluoromethyl)-3'-ethoxy-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 279)** was synthesized according to the procedures described for the preparation of Example A3 (step **A** and **D**) by using cyclopropanol in step **B** and 2-(2-(difluoromethyl)-3-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in step **D**. LC-MS: m/z 462.2 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.37 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.84 - 6.79 (m, 2H), 6.76 - 6.61 (m, 2H), 6.41 (t, J = 54.0 Hz, 1H), 4.22 - 4.11 (m, 4H), 3.85 - 3.74 (m, 4H), 3.24 - 3.04 (m, 1H), 2.28 - 2.17 (m, 2H), 2.01 - 1.92 (m, 2H), 1.43 (t, J = 6.8 Hz, 3H), 0.31 - 0.21 (m, 4H).

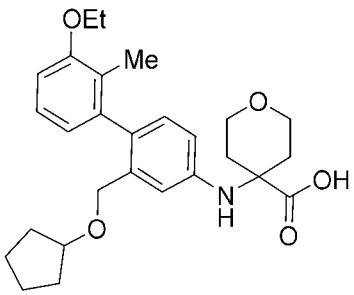
Example A30

4-((2-((cyclopentyloxy)methyl)-3'-ethoxy-2'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 229)





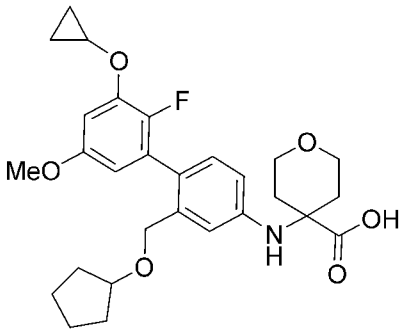
[0497] 2-(3-ethoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesized according to the procedures described for the preparation of **22-3** (step **A** and **B** in Example **A24**) by using 3-bromo-2-methylphenol in step **A**. LC-MS: m/z 263.2 $(M+H)^+$.

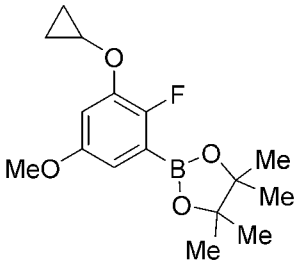


[0498] 4-((2-((cyclopentyloxy)methyl)-3'-ethoxy-2'- methyl -[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (**Compound 229**) was synthesized according to the procedures described for the preparation of Example A3 (step **B** and **D**) by using cyclopentanol in step **B**, 2-(3-ethoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in step **D**. LC-MS: m/z 454.1 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.08 (t, J = 7.6 Hz, 1H), 6.86 - 6.79 (m, 3H), 6.66 - 6.63 (m, 2H), 4.10 - 4.00 (m, 4H), 3.84 - 3.74 (m, 5H), 2.26 - 2.19 (m, 2H), 2.10 - 2.02 (m, 2H), 1.88 (s, 3H), 1.57 - 1.40 (m, 11H).

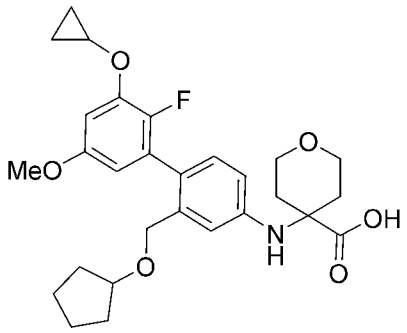
Example A31

4-((2-((cyclopentyloxy)methyl)-3'-cyclopropoxy-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 249)





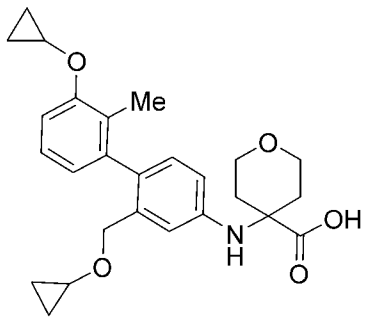
[0499] 2-[3-(cyclopropyloxy)-2-fluoro-5-methoxyphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesized according to the procedures described for the preparation of **25-5** (step **A** to **D** in Example **A27**) by using 2-fluoro-5-methoxyphenol in step **A**. LC-MS: m/z 309.2 $(M+H)^+$.

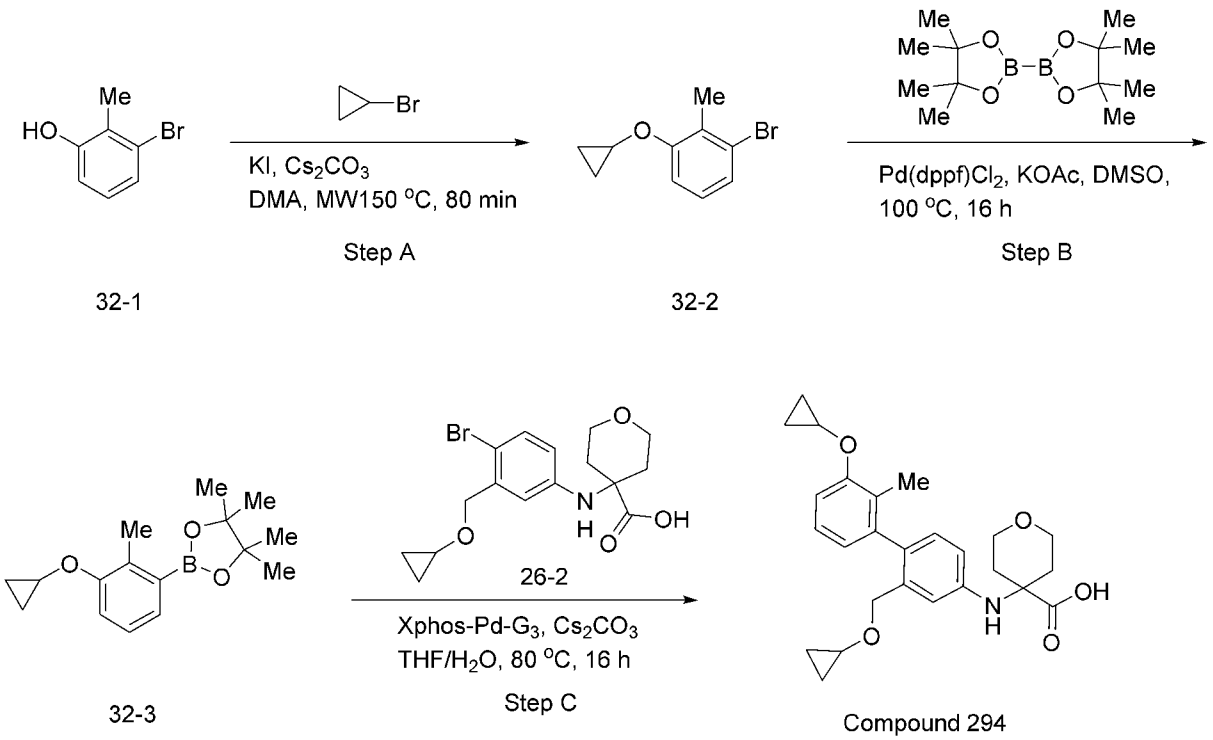


[0500] 4-((2-((cyclopentyloxy)methyl)-3'-cyclopropoxy-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid **(Compound 249)** was synthesized according to the procedures described for the preparation of Example **A3** (step **A** and **D**) by using cyclopentanol in step **B** and 2-[3-(cyclopropyloxy)-2-fluoro-5-methoxyphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in step **D**. LC-MS: m/z 500.1 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.96 (d, J = 8.8 Hz, 1H), 6.90 (dd, J = 6.4, 2.8 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 8.4, 2.4 Hz, 1H), 6.90 (dd, J = 5.2, 3.6 Hz, 1H), 4.23 (s, 2H), 3.90 - 3.78 (m, 9H), 2.28 - 2.21 (m, 2H), 2.02 - 1.99 (m, 2H), 1.61 - 1.47 (m, 8H), 0.84 - 0.78 (m, 4H).

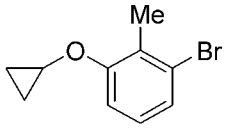
Example A32

4-((3'-cyclopropoxy-2-(cyclopropoxymethyl)-2'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 294)



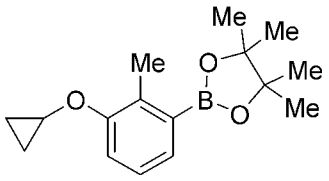


[0501] Step A 1-bromo-3-cyclopropoxy-2-methylbenzene



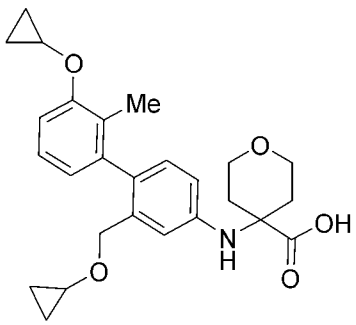
[0502] The mixture of 3-bromo-2-methylphenol (2 g, 10.7 mmol), bromocyclopropane (5.17 g, 43 mmol), Cs_2CO_3 (6.97 g, 21.39 mmol) and KI (355 mg, 2.14 mmol) in DMA (20 mL) was heated at 150 °C for 80 min under Biotage microwave. After cooling, the mixture was diluted with brine (100 mL) and extracted with EtOAc (50 mL x 2). The organic layers were washed with brine (20 mLx3), dried over anhydrous Na2SO4, filtered, and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 100% PE gradient @ 100 mL/min) to give 1-bromo-3-cyclopropoxy-2-methylbenzene (1.5 g, 61.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 - 7.14 (m, 2H), 7.01 (t, J = 8.0 Hz, 1H), 3.83 - 3.60 (m, 1H), 2.26 (s, 3H), 0.79 - 0.77 (m, 4H).

[0503] Step B 2-(3-cyclopropoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0504] To a solution of 1-bromo-3-cyclopropoxy-2-methylbenzene (1.5 g, 6.61 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.01 g, 7.93 mmol) in DMSO (10 mL) was added Pd(dppf)Cl_2 (483 mg, 661 umol) and KOAc (1.30 g, 13.2 mmol). The mixture was stirred at 100 °C for 16 h. After cooling, the reaction mixture was poured into H_2O (120 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (60 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 100% PE gradient @ 100 mL/min) to give 2-(3-cyclopropoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.24 g, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 8.0 Hz, 1H), 4.02 - 3.99 (m, 1H), 2.20 (s, 3H), 1.24 (s, 12H), 0.70 - 0.66 (m, 2H), 0.59 - 0.55 (m, 2H).

[0505] 4-((3'-cyclopropoxy-2-(cyclopropoxymethyl)-2'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid

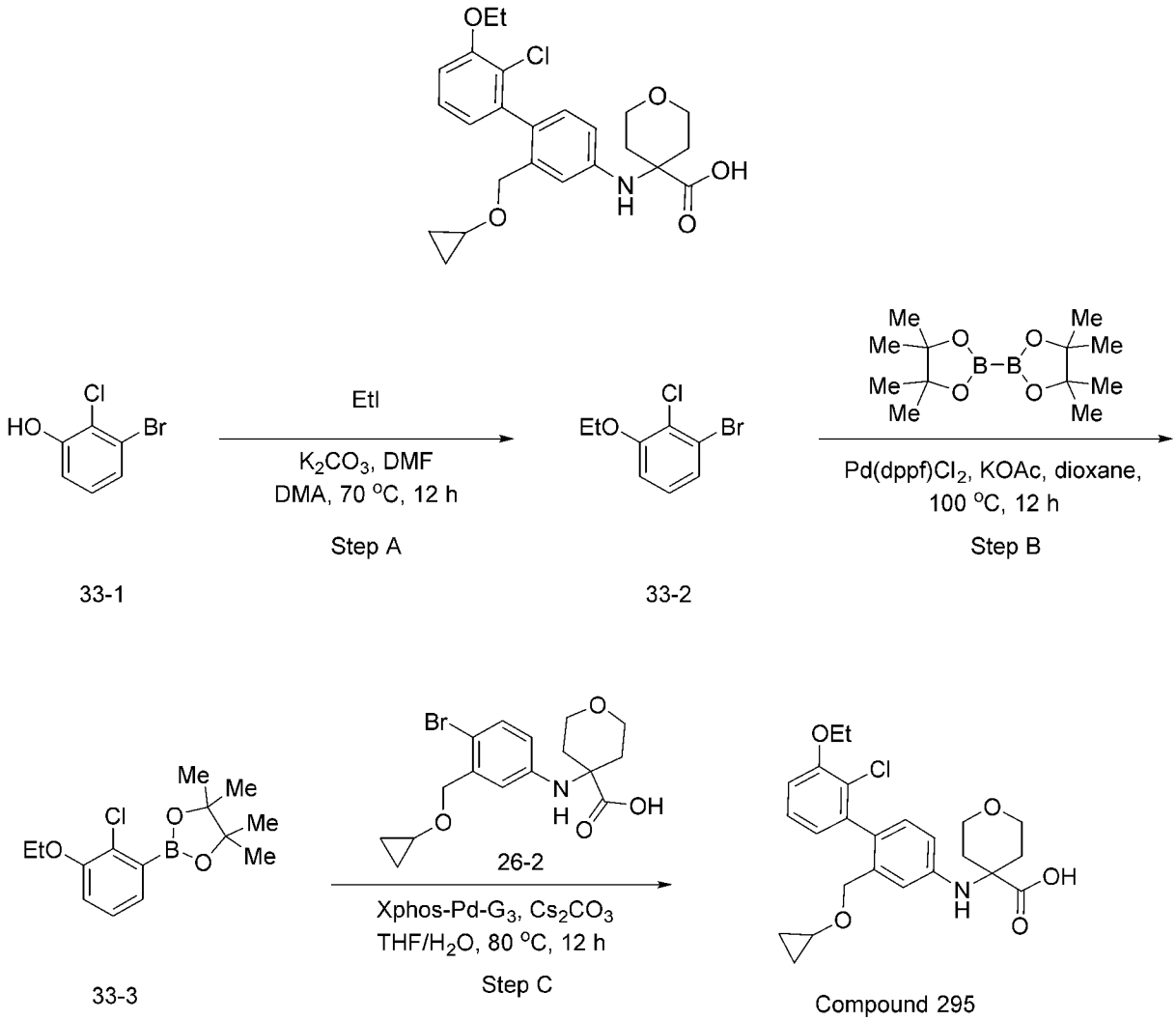


[0506] To a solution of 4-[4-bromo-3-(cyclopropoxymethyl)anilino]tetrahydropyran-4-carboxylic acid (1.4 g, 3.78 mmol) and 2-(3-cyclopropoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.14 g, 4.16 mmol) in THF (8 mL) and H_2O (4 mL) was added XPhos Pd G3 (320 mg, 378 umol) and Cs_2CO_3 (2.46 g, 7.56 mmol). The mixture was stirred at 80 °C for 16 h. The mixture was adjusted with 1N HCl to pH =5, extracted with EtOAc (100 mLx2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by *prep*. HPLC (column: Xtimate C18 150*40mm*10um; mobile phase: [water ($NH_3 \cdot H_2O$+NH_4HCO_3)-CH_3CN]; B%: 25%-55%, 8 min) to give 4-((3'-cyclopropoxy-2-(cyclopropoxymethyl)-2'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (586.7 mg, 35.46% yield). LC-MS: m/z 438.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 7.20 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.79 - 6.76 (m, 2H),

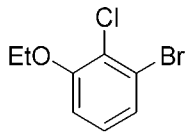
6.65 - 6.62 (m, 2H), 4.16 - 4.10 (m, 2H), 3.83 - 3.75 (m, 5H), 3.16 - 3.12 (m, 1H), 2.24 - 2.18 (m, 2H), 1.98 - 1.95 (m, 2H), 1.78 (s, 3H), 0.79 - 0.71 (m, 2H), 0.69 - 0.67 (m, 2H), 0.28 - 0.23 (m, 4H).

Example A33

4-((2'-chloro-2-(cyclopropoxymethyl)-3'-ethoxy-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 295)

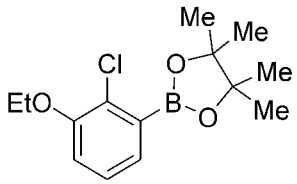


[0507] Step A 1-bromo-2-chloro-3-ethoxybenzene



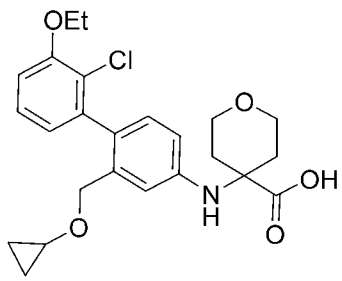
[0508] To a solution of 3-bromo-2-chlorophenol (10 g, 48.2 mmol) in DMF (30 mL) was added EtI (15.0 g, 96.4 mmol) and K_2CO_3 (13.3 g, 96.4 mmol). The mixture was stirred at 70 °C for 12 h. After cooling, the reaction mixture was diluted with water (100 mL) and then extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~4% EtOAc/PE @ 100 mL/min) to give 1-bromo-2-chloro-3-ethoxybenzene (11 g, 96.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 8.2, 1.2 Hz, 1H), 7.07 (t, J = 8.2 Hz, 1H), 6.89 - 6.84 (m, 1H), 4.10 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H).

[0509] Step B 2-(2-chloro-3-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0510] To a solution of 1-bromo-2-chloro-3-ethoxy-benzene (11 g, 46.7 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (13.1 g, 51.4 mmol) in dioxane (100 mL) was added Pd(dppf)Cl_2 (3.42 g, 4.67 mmol) and KOAc (13.8 g, 140 mmol). The mixture was stirred at 100 °C for 12 h. The reaction mixture was quenched by addition water (100 mL), then extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~12% EtOAc/PE gradient @ 100 mL/min) to give 2-(2-chloro-3-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.5 g, 64.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 - 7.14 (m, 2H), 6.98 (dd, J = 8.0, 1.6 Hz, 1H), 4.13 - 4.06 (m, 2H), 1.45 (t, J = 7.0 Hz, 3H), 1.37 (s, 12H).

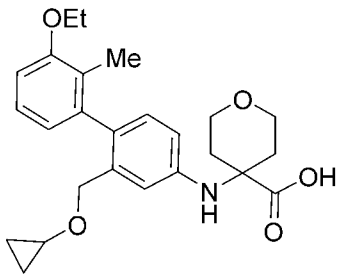
[0511] 4-((2'-chloro-2-(cyclopropoxymethyl)-3'-ethoxy-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (**Compound 295**)

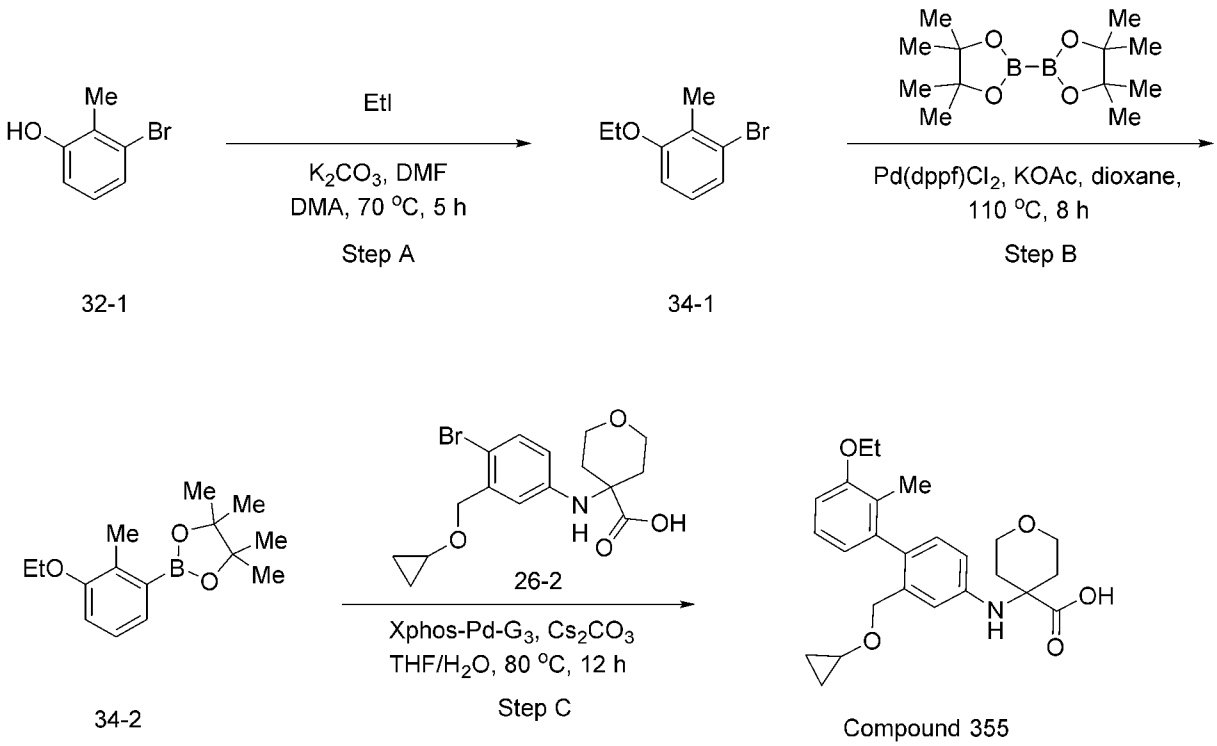


[0512] To a solution of 4-[4-bromo-3-(cyclopropoxymethyl)anilino]tetrahydropyran-4-carboxylic acid (0.5 g, 1.35 mmol) and 2-(2-chloro-3-ethoxy-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (420 mg, 1.49 mmol) in THF (15 mL) and H_2O (4 mL) was added XPhos Pd G3 (229 mg, 270 umol) and Cs_2CO_3 (1.32 g, 4.05 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by addition water (20 mL), acidified with 1N HCl to *p*H = 5 and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by *prep*. HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water ($NH_3 \cdot H_2O$+NH_4HCO_3)-CH_3CN]; B%: 28%-58%, 7 min) to give 4-((2'-chloro-2-(cyclopropoxymethyl)-3'-ethoxy-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (286 mg, 47% yield). LC-MS: m/z 446.2 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.99 (t, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.62 -6.55 (m, 3H), 6.42 (dd, J = 8.0, 2.4 Hz, 1H), 4.05 - 3.90 (m, 2H), 3.91 - 3.89 (m, 2H), 3.60 - 3.52 (m, 4H), 2.99 - 2.92 (m, 1H), 2.05 - 1.97 (m, 2H), 1.78 - 1.74 (m, 2H), 1.22 (t, J = 7.0 Hz, 3H), 0.12 - 0.01 (m, 4H).

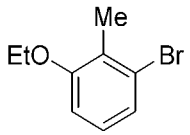
Example A34

4-((2-(cyclopropoxymethyl)-3'-ethoxy-2'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 355)



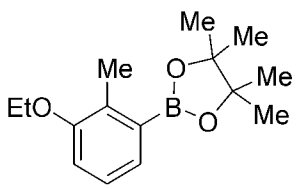


[0513] Step A 1-bromo-3-ethoxy-2-methylbenzene



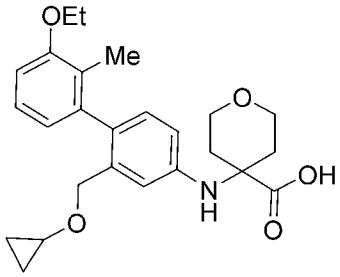
[0514] To a solution of 3-bromo-2-methyl-phenol (3 g, 16.0 mmol) in DMF (30 mL) was added EtI (2.50 g, 16.0 mmol, 1.28 mL) and K_2CO_3 (5.54 g, 40.1 mmol). The mixture was stirred at 70 °C for 5 h. The mixture was diluted with water (120 mL), extracted with ethyl acetate (50 mL x 2). The combined organic phase were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~1% EtOAc/PE ether gradient at 100 mL/min) to give 1-bromo-3-ethoxy-2-methyl-benzene (2.9 g, 84.1% yield).

[0515] Step B 2-(3-ethoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0516] To a solution of 1-bromo-3-ethoxy-2-methyl-benzene (2.9 g, 13.5 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4.11 g, 16.2 mmol) in dioxane (50 mL) was added Pd(dppf)Cl_2 (987 mg, 1.35 mmol) and KOAc (2.65 g, 27.0 mmol). The mixture was stirred at 110 °C for 8 h. The reaction mixture was cooled to room temperature. The reaction mixture diluted with water (100 mL) and extracted with ethyl acetate (60 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~2% EtOAc/PE gradient @ 100 mL/min) to give 2-(3-ethoxy-2-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.8 g, 79.2% yield). LC-MS: m/z 262.9 $(M+H)^+$.

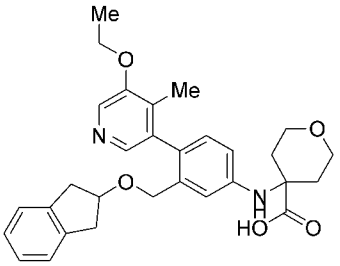
[0517] Step C 4-((2-(cyclopropoxymethyl)-3'-ethoxy-2'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (Compound 355)



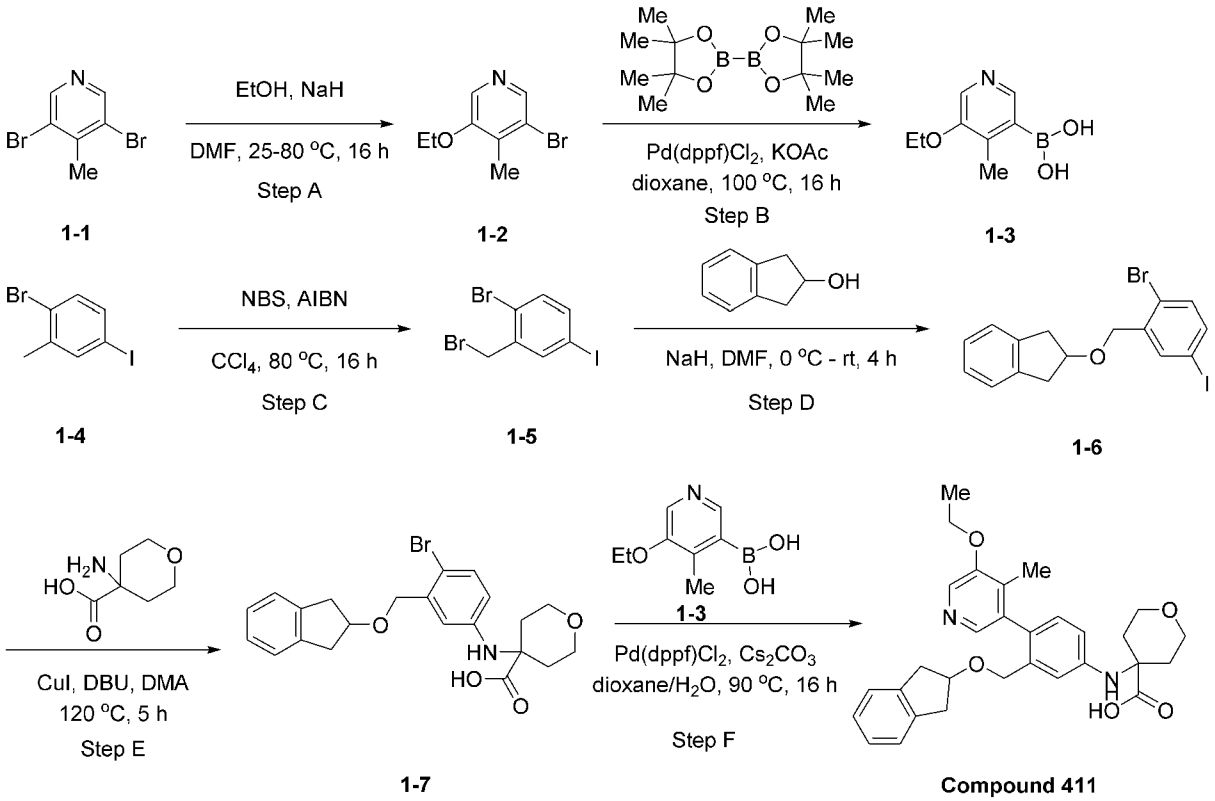
[0518] To a solution of 2-(3-ethoxy-2-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (212 mg, 810 umol) and 4-((4-bromo-3-(cyclopropoxymethyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (150 mg, 405) in THF (3 mL) and H_2O (2 mL) was added XPhos Pd G3 (34.3 mg, 40.5 umol) and Cs_2CO_3 (264 mg, 810 umol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with water (30 mL), acidified with 1N HCl to *p*H = 5, extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient at 100 mL/min) and further purified by purified by *prep*. HPLC (column: Welch Xtimate C18 150*30mm*5μm; mobile phase: [water ($NH_3 \cdot H_2O$+NH_4HCO_3)-CH_3CN]; B%: 25%-55%, 7 min) to give the product 4-((2-(cyclopropoxymethyl)-3'-ethoxy-2'-methyl-[1,1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-4-carboxylic acid (16.15 mg, 9.3% yield). LC-MS: m/z 426.5 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.08 (t, J = 8.0 Hz, 1H), 6.86 - 6.77 (m, 3H), 6.68 - 6.62 (m, 2H), 4.19 - 4.05 (m, 4H), 3.82 - 3.75 (m, 4H), 3.18 - 3.13 (m, 1H), 2.26 - 2.19 (m, 2H), 1.99 - 1.94 (m, 2H), 1.86 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H), 0.29 - 0.26 (m, 4H).

Example A35

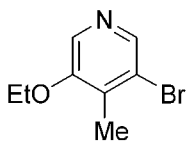
4-({3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-4-(5-ethoxy-4-methylpyridin-3-yl)phenyl}amino)oxane-4-carboxylic acid (Compound 411)



Compound 411

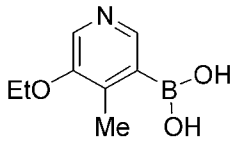


[0519] Step A: 3-bromo-5-ethoxy-4-methylpyridine



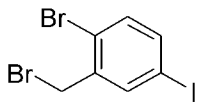
[0520] NaH (2.87 g, 71.7 mmol, 60% in mineral oil) was added to EtOH (25 mL) at 25 °C. After being stirred for 0.5 h, then a solution of 3,5-dibromo-4-methylpyridine (10 g, 39.9 mmol) in DMF (100 mL) was added. The resulting mixture was heated to 80 °C and stirred for 16 h. After cooling, the reaction mixture was quenched by ice cold water (100 mL), extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (120 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/PE gradient @ 100 mL/min) to give 3-bromo-5-ethoxy-4-methylpyridine (6.1 g, 70.8% yield). LC-MS: m/z 217.4 $(M+H)^+$.

[0521] Step B: (5-ethoxy-4-methylpyridin-3-yl)boronic acid



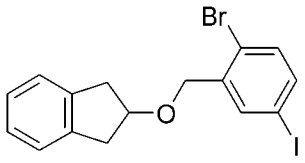
[0522] To the mixture of 3-bromo-5-ethoxy-4-methyl-pyridine (3.0 g, 13.9 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4.58 g, 18.1 mmol) in dioxane (10 mL), was added KOAc (4.09 g, 41.7 mmol), $Pd(dppf)Cl_2$ (1.02 g, 1.39 mmol). After being degassed and purged with nitrogen three times. The reaction mixture was stirred at 100 °C for 16 h under nitrogen atmosphere. After cooling, the reaction was filtered and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (80 g SepaFlash® Silica Flash Column, Eluent of 0~20% MeOH/DCM gradient @ 40 mL/min) to give a crude. This crude was further triturated with PE/EtOAc (V/V=10:1, 50 mL) to give (5-ethoxy-4-methyl-3-pyridyl)boronic acid (2.44 g, 97.1% yield). LC-MS: m/z 182.2 $(M+H)^+$.

[0523] Step C: 1-bromo-2-(bromomethyl)-4-iodobenzene



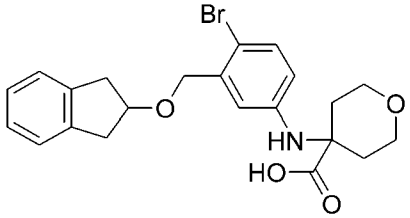
[0524] The mixture of bromo-4-iodo-2-methylbenzene (20.0 g, 67.36 mmol), AIBN (5.53 g, 33.68 mmol) and NBS (11.99 g, 67.36 mmol) in CCl_4 (300 mL) was heated to 80 °C and stirred for 16 h. After cooling to room temperature, the reaction mixture was concentrated. The residue was purified by silica gel column (100% PE) to afford 1-bromo-2-(bromomethyl)-4-iodobenzene (8.0 g, 31.6% yield).

[0525] Step D: 2-[(2-bromo-5-iodophenyl)methoxy]-2,3-dihydro-1H-indene



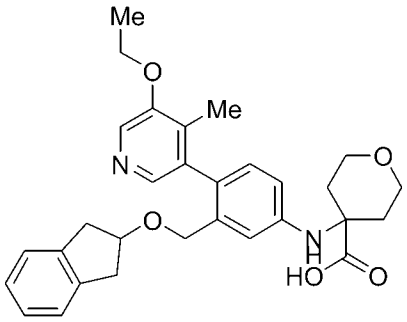
[0526] To the solution of 2,3-dihydro-1H-inden-2-ol (0.86 g, 6.39 mmol) in DMF (40 mL), was added NaH (319 mg, 7.98 mmol, 60% in mineral oil) under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Then a solution of 1-bromo-2-(bromomethyl)-4-iodobenzene (2.00 g, 5.32 mmol) in DMF (10 mL) was added into the above solution. The reaction mixture was stirred at room temperature for 3 h. Then the reaction mixture was quenched with *sat. aq.* NH_4Cl (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (0~10% EtOAc in PE) to afford 2-[(2-bromo-5-iodophenyl)methoxy]-2,3-dihydro-1H-indene (450 mg, 19.7% yield).

[0527] Step E: 4-((4-bromo-3-(((2,3-dihydro-1H-inden-2-yl)oxy)methyl)phenyl)amino) tetrahydro-2H-pyran-4-carboxylic acid



[0528] To a solution of 2-[(2-bromo-5-iodophenyl)methoxy]-2,3-dihydro-1H-indene (450 mg, 1.05 mmol) in DMAc (10 mL) was added CuI (40 mg, 0.21 mmol), 4-aminotetrahydro-2H-pyran-4-carboxylic acid (304 mg, 2.10 mmol) and DBU (93.13 mg, 0.61 mmol). The resulting mixture was stirred at 120 °C for 5 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature, poured into water (20 mL). The *p*H value was adjusted to 7 by acetic acid. The resulting mixture was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (0-10% MeOH in CH_2Cl_2) to afford 4-({4-bromo-3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]phenyl}amino)oxane-4-carboxylic acid (35 mg, 44.9% yield). LC-MS: m/z 447.9 $(M+H)^+$.

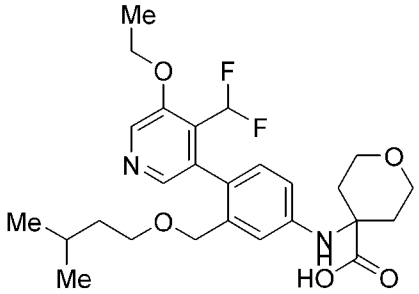
[0529] Step F: 4-({3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-4-(5-ethoxy-4-methylpyridin-3-yl)phenyl}amino)oxane-4-carboxylic acid (**Compound 411**)



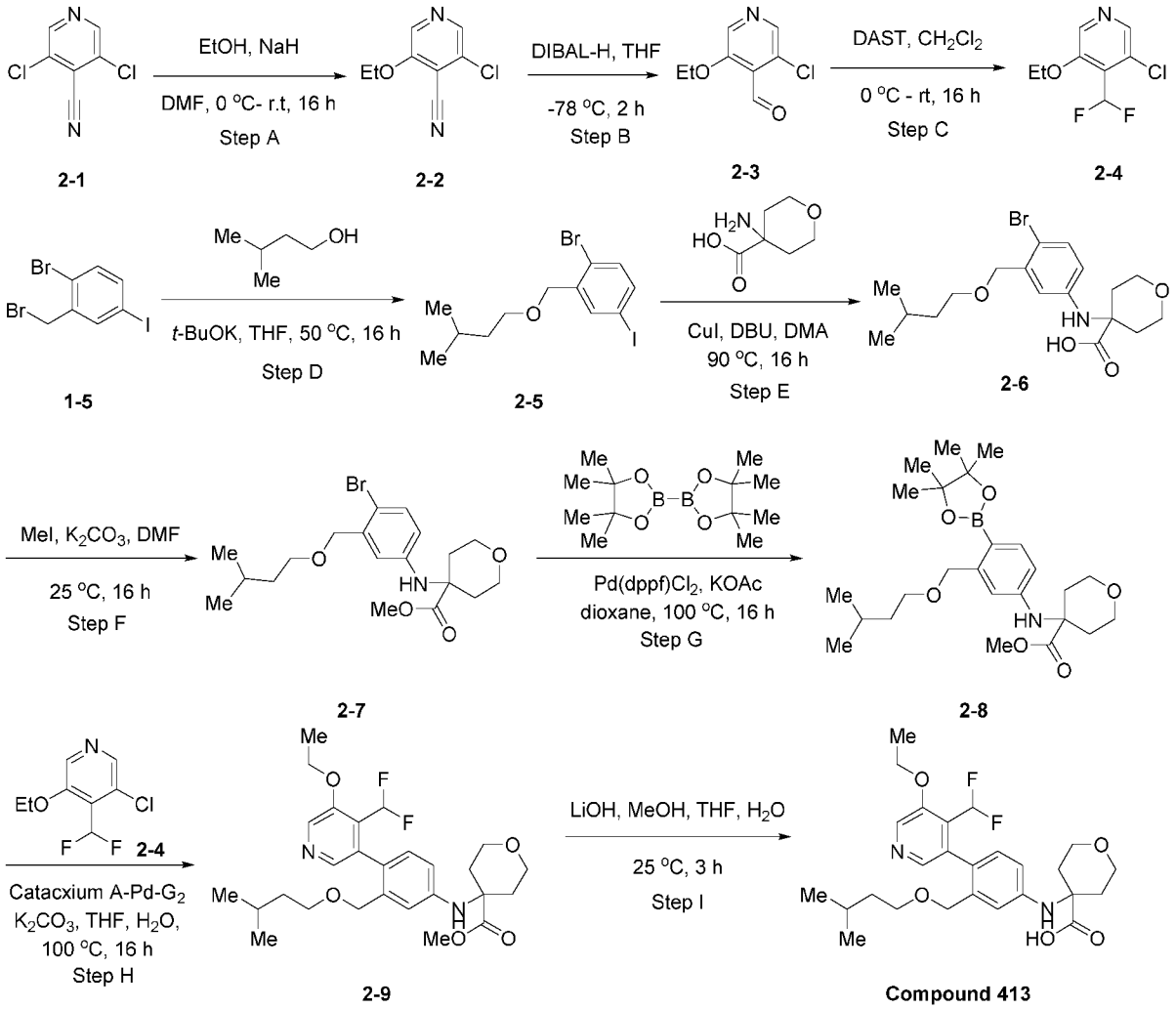
[0530] To the mixture of 4-((4-bromo-3-(((2,3-dihydro-1H-inden-2-yl)oxy) methyl)phenyl)amino) tetrahydro-2H-pyran-4-carboxylic acid (225 mg, 0.504 mmol), (5-ethoxy-4-methyl-3-pyridyl)boronic acid (365 mg, 2.02 mmol) in H_2O (1 mL) and dioxane (4 mL), was added Cs_2CO_3 (329 mg, 1.01 mmol) and $Pd(dppf)Cl_2$ (73.8 mg, 101 μmol). After being degassed and purged with N_2 for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N_2 atmosphere. After cooling, the mixture was diluted with water (10 mL), acidified with 1M *aq*. HCl to *p*H = 5, extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM gradient @ 20 mL/min) and further purified by *prep*. HPLC (Phenomenex C18 80*40mm*5 μm; Mobile Phase A: Water (0.05% $NH_3 \cdot H_2O$+10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 40 mL/min; Gradient: 25% B to 55% B in 7 min) to give 4-({3-[(2,3-dihydro-1H-inden-2-yloxy)methyl]-4-(5-ethoxy-4-methylpyridin-3-yl)phenyl}amino)oxane-4-carboxylic acid (20.6 mg, 7.7 % yield). LC-MS: m/z 503.6 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.88 (s, 1H), 7.13 - 7.07 (m, 4H), 6.87 - 6.82 (m, 2H), 6.67 (dd, J = 8.2, 2.0 Hz, 1H), 4.23 - 4.10 (m, 5H), 3.85 - 3.74 (m, 4H), 3.04 - 2.93 (m, 2H), 2.73 (dd, J = 16.2, 4.0 Hz, 1H), 2.64 (dd, J = 16.2, 4.0 Hz, 1H), 2.26 - 2.19 (m, 2H), 2.04 - 1.98 (m, 2H), 1.93 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H).

Example A36

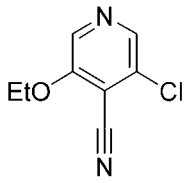
4-({4-[4-(difluoromethyl)-5-ethoxypyridin-3-yl]-3-[(3-methylbutoxy)methyl] phenyl}amino) oxane-4-carboxylic acid (Compound 413)



Compound 413

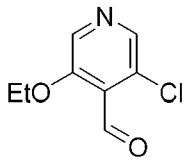


[0531] Step A: 3-chloro-5-ethoxyisonicotinonitrile



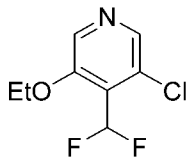
[0532] To a solution of EtOH (2.53 g, 55 mmol) in DMF (25 mL) was added NaH (2.20 g, 55 mmol, 60% in mineral oil) at 0 °C. After being stirred for 0.5 h, 3,5-dichloroisonicotinonitrile (10.0 g, 57.8 mmol) was added. The resulting reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated. The residue was diluted with brine (100 mL), extracted with EtOAc (100 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (80 g SepaFlash®Silica Flash Column, Eluent of 0~40% EtOAc/PE gradient @ 50 mL/min) to give 3-chloro-5-ethoxyisonicotinonitrile (1.5 g, 14.2% yield). LC-MS: m/z 183.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.34 (s, 1H), 4.31 (q, J = 7.0 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H).

[0533] Step B: 3-chloro-5-ethoxyisonicotinaldehyde



[0534] To a solution of 3-chloro-5-ethoxyisonicotinonitrile (1.0 g, 5.48 mmol) in DCM (30 mL) was added DIBAL-H (7.30 mL, 10.95 mmol, 1.5 M solution in toluene) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. Then the reaction mixture quenched with saturated potassium sodium tartrate solution, extracted with DCM (100 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (40 g SepaFlash®Silica Flash Column, Eluent of 0~20% EtOAc/PE@ 50 mL/min) to give 3-chloro-5-ethoxyisonicotinaldehyde (380 mg, 37.4% yield). LC-MS: m/z 186.0 $(M+H)^+$.

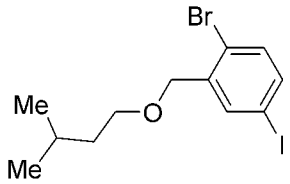
[0535] Step C: 3-chloro-4-(difluoromethyl)-5-ethoxypyridine



[0536] To the ice water cooled solution of 3-chloro-5-ethoxyisonicotinaldehyde (380 mg, 2.05 mmol) in DCM (5 mL) was added DAST (406 uL, 3.07 mmol). The reaction mixture was stirred at 25 °C for 16

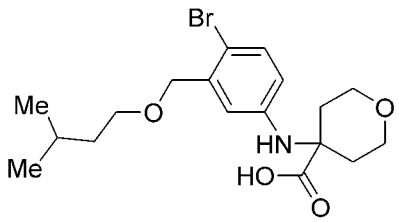
h. The reaction mixture was diluted with *sat.aq*.$NaHCO_3$ (50 mL), extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (4 g SepaFlash®Silica Flash Column, Eluent of 10~40% EtOAc/PE gradient@ 50 mL/min) to give 3-chloro-4-(difluoromethyl)-5-ethoxypyridine (380 mg, 89.2% yield). LC-MS: m/z 208.1 $(M+H)^+$.

[0537] Step D: 1-bromo-4-iodo-2-((isopentyloxy)methyl)benzene



[0538] To a solution of 1-bromo-2-(bromomethyl)-4-iodo-benzene (2 g, 5.32 mmol) and 3-methylbutan-1-ol (469 mg, 5.32 mmol) in THF (6 mL) was added *t*-BuOK (896 mg, 7.98 mmol). The reaction mixture was heated to 50 °C and stirred for 16 h. After concentration, the residue was diluted with brine (30 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (40 g SepaFlash®Silica Flash Column, Eluent of 100% PE gradient@ 50 mL/min) to give 1-bromo-4-iodo-2-((isopentyloxy)methyl)benzene (1.7 g, 83.4% yield).

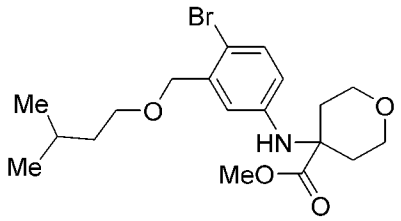
[0539] Step E: 4-((4-bromo-3-((isopentyloxy)methyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid



[0540] To a solution of 1-bromo-4-iodo-2-((isopentyloxy)methyl)benzene (1.7 g, 4.44 mmol) and 4-aminotetrahydro-2H-pyran-4-carboxylic.acid (1.29 g, 8.9 mmol) in DMA (15 mL) was added CuI (169 mg, 888 μmol) and DBU (2.03 g, 13.3 mmol). The reaction mixture was stirred at 90 °C for 16 h. After concentration, the residue was diluted with water (20 mL), acidified by 1M *aq*.HCl to *p*H=6, extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (40 g SepaFlash®Silica Flash Column, Eluent of 0~10% MeOH/DCM gradient) to give 4-((4-bromo-3-

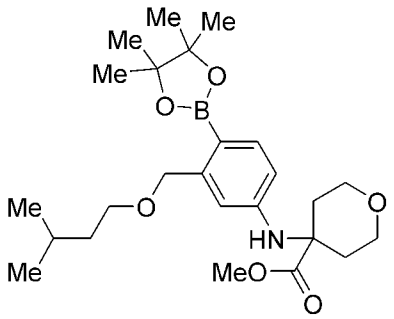
((isopentyloxy)methyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (1.0 g, 56.3% yield). LC-MS: m/z 400.2 $(M+H)^+$.

[0541] Step F: methyl 4-((4-bromo-3-((isopentyloxy)methyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylate



[0542] To a solution of 4-((4-bromo-3-((isopentyloxy)methyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (1.0 g, 2.50 mmol) and MeI (187 uL, 3.00 mmol) in DMF (10 mL) was added K_2CO_3 (863 mg, 6.25 mmol). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (40 g SepaFlash®Silica Flash Column, Eluent of 10~40% EtOAc/PE gradient@ 50 mL/min) to give methyl 4-[4-bromo-3-(isopentyloxymethyl)anilino]tetrahydropyran-4-carboxylate (1.03 g, 99.6% yield). LC-MS: m/z 414.3 $(M+H)^+$.

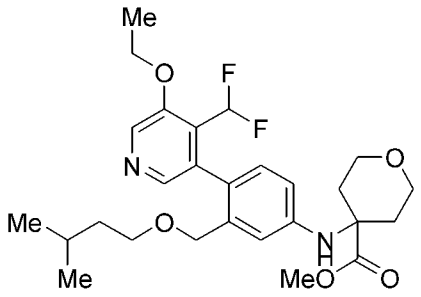
[0543] Step G: methyl 4-((3-((isopentyloxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylate



[0544] To a solution of methyl 4-[4-bromo-3-(isopentyloxymethyl)anilino]tetrahydropyran-4-carboxylate (1.03 g, 2.49 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (758 mg, 3 mmol) in dioxane (10 mL) was added KOAc (488 mg, 4.97 mmol) and $Pd(dppf)Cl_2$ (182 mg, 249 μmol). The reaction mixture was stirred at 100 °C for 16 h. After cooling and concentration, the residue was purified by flash silica gel chromatography (24 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/PE gradient @ 50 mL/min) to give methyl 4-[3-(isopentyloxymethyl)-

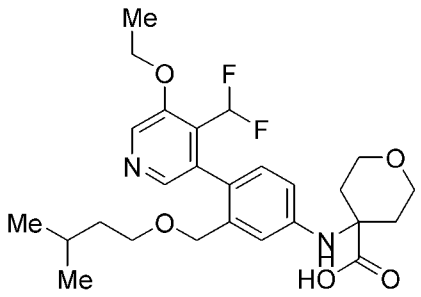
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]tetrahydropyran-4-carboxylate (200 mg, 17.4% yield). LC-MS: m/z 462.3 $(M+H)^+$.

[0545] Step H: methyl 4-((4-(4-(difluoromethyl)-5-ethoxypyridin-3-yl)-3-((isopentyloxy)methyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylate



[0546] To the solution of methyl 4-[3-(isopentyloxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]tetrahydropyran-4-carboxylate (111 mg, 241 μmol) and 3-chloro-4-(difluoromethyl)-5-ethoxypyridine (50 mg, 241 μmol) in THF (2 mL) and H_2O (0.2 mL) was added Catacxium A-Pd-G2 (16.1 mg, 24.1 μmol) and K_2CO_3 (66.6 mg, 482 μmol). The reaction mixture was stirred at 80°C under nitrogen for 16 h. The reaction mixture was concentrated. The residue was diluted with brine (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (4 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/PE gradient @ 20 mL/min) to give methyl 4-((4-(4-(difluoromethyl)-5-ethoxypyridin-3-yl)-3-((isopentyloxy)methyl)phenyl)amino)tetrahydro-2H-pyran-4-carboxylate (60 mg, 48.9% yield). LC-MS: m/z 507.4 $(M+H)^+$.

[0547] Step I: 4-({4-[4-(difluoromethyl)-5-ethoxypyridin-3-yl]-3-[(3-methylbutoxy)methyl] phenyl}amino) oxane-4-carboxylic acid **(Compound 413)**

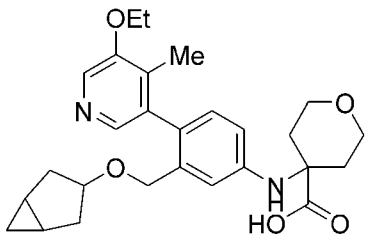


[0548] To a solution of methyl 4-[4-[4-(difluoromethyl)-5-ethoxy-3-pyridyl]-3-(isopentyloxymethyl)anilino]tetrahydropyran-4-carboxylate (60 mg, 118 μmol) and in MeOH (4 mL), THF (1 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (24.9 mg, 592 μmol). The reaction mixture was

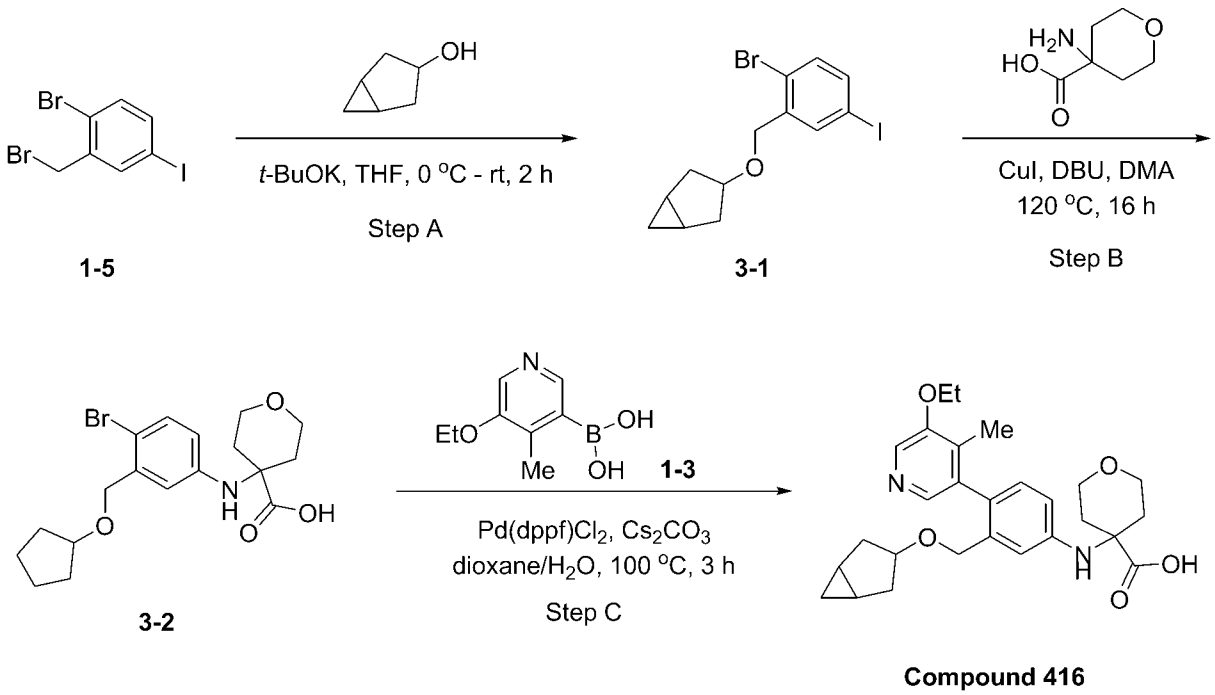
stirred at 25 °C for 3 h. After concentration, the residue was diluted with water (20 mL), acidified with 1 M *aq*. HCl to *p*H=6, extracted with EtOAc (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was purified by *prep*. HPLC (Column: Boston Prime C18 150*30mm*5um; Mobile Phase A: Water (0.05% $NH_3.H_2O$+10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 40 mL/min; Gradient: 30% B to 60% B in 7 min) to give 4-({4-[4-(difluoromethyl)-5-ethoxypyridin-3-yl]-3-[(3-methylbutoxy)methyl] phenyl}amino) oxane-4-carboxylic acid (8 mg, 13.3% yield). LC-MS: m/z 493.6 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.41 (s, 1H), 8.05 (s, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 6.72 - 6.42 (m, 2H), 4.31 (q, J = 6.8 Hz, 2H), 4.14 (q, J = 11.5 Hz, 2H), 3.91 - 3.74 (m, 4H), 3.29 (t, J = 6.6 Hz, 2H), 2.35 - 2.17 (m, 2H), 2.11 - 1.96 (m, 2H), 1.64 - 1.54 (m, 1H), 1.49 (t, J = 7.0 Hz, 3H), 1.34 (q, J = 6.6 Hz, 2H), 0.84 (dd, J = 6.6, 1.2 Hz, 6H).

Example A37

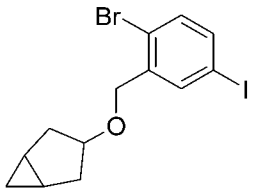
4-{[3-({bicyclo[3.1.0]hexan-3-yloxy}methyl)-4-(5-ethoxy-4-methylpyridin-3-yl)phenyl]amino} oxane-4-carboxylic acid (Compound 416)



Compound 416

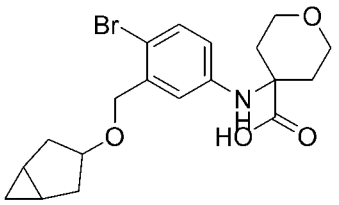


[0549] Step A: 3-((2-bromo-5-iodobenzyl)oxy)bicyclo[3.1.0]hexane



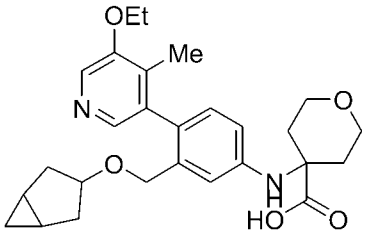
[0550] To a solution of bicyclo[3.1.0]hexan-3-ol (887.9 mg, 9.05 mmol) in THF (20 mL) was added *t*-BuOK (1.52 g, 13.57 mmol) at 0 °C. After being stirred at 0 °C for 30 min under nitrogen, a solution of 1-bromo-2-(bromomethyl)-4-iodo-benzene (1.7 g, 4.52 mmol) in THF (8 mL) was added in dropwise. After addition, the resulting mixture was stirred at 25 °C for 2 h. Then the mixture was quenched with H_2O (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (40 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/PE gradient @ 50 mL/min) to afford 3-[(2-bromo-5-iodo-phenyl)methoxy]bicyclo[3.1.0]hexane (1.19 g, 66.9% yield). ^{1}H NMR (400MHz, CD_3OD) δ 7.53 (d, J = 2.4 Hz, 1H), 7.30 (dd, J = 2.4, 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 4.16 (s, 2H), 3.88 (t, J = 6.4 Hz, 1H), 1.90 - 1.81 (m, 2H), 1.79 - 1.72 (m, 2H), 1.11 - 1.06 (m, 2H), 0.36 - 0.29 (m, 1H), 0.28 - 0.20 (m, 1H).

[0551] Step B: 4-((3-((bicyclo[3.1.0]hexan-3-yloxy)methyl)-4-bromophenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid



[0552] To a solution of 3-[(2-bromo-5-iodo-phenyl)methoxy]bicyclo[3.1.0]hexane (500 mg, 1.27 mmol) and 4-aminotetrahydropyran-4-carboxylic acid (369.30 mg, 2.54 mmol) in DMA (8 mL), was added DBU (0.7 mL, 4.45 mmol) and CuI (48.45 mg, 254.42 μmol). The reaction mixture was stirred at 120 °C for 16 h. After cooling, the reaction mixture was poured into water (50 mL), neutralized with 1M *aq*. HCl to *p*H = 7, extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (12 g SepaFlash® Silica Flash Column, Eluent of 0~50% EtOAc/PE gradient @ 50 mL/min) to afford 4-[3-(3-bicyclo[3.1.0]hexanyloxymethyl)-4-bromo-anilino]tetrahydropyran-4-carboxylic acid (400 mg, 74.7% yield). LC-MS: m/z 409.7 $(M+H)^+$.

[0553] Step C: 4-{[3-({bicyclo[3.1.0]hexan-3-yloxy}methyl)-4-(5-ethoxy-4-methylpyridin-3-yl)phenyl]amino}oxane-4-carboxylic acid (**Compound 416**)



[0554] To a solution of 4-((3-((bicyclo[3.1.0]hexan-3-yloxy)methyl)-4-bromophenyl)amino)tetrahydro-2H-pyran-4-carboxylic acid (70 mg, 171 μmol) and (5-ethoxy-4-methylpyridin-3-yl)boronic acid (123 mg, 682 μmol) in dioxane (1 mL) and H_2O (0.25 mL) was added $Pd(dppf)Cl_2$ (24.9 mg, 34.1 μmol) and Cs_2CO_3 (111 mg, 341 μmol). The reaction mixture was stirred at 100 °C for 16 h under nitrogen. After cooling, the reaction mixture was diluted with water (5 mL), acidified by 2M *aq*. HCl to *p*H=6, extracted with EtOAc (5 mL x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*. HPLC (Column: Phenomenex C18 80*40mm*3um; Mobile Phase A: Water (0.05% $NH_3.H_2O$+10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 40 mL/min; Gradient: 25% B to 55% B in 7 min) to give 4-{[3-({bicyclo[3.1.0]hexan-3-yloxy}methyl)-4-(5-ethoxy-4-methylpyridin-3-yl)phenyl]amino} oxane-4-carboxylic acid (9.32 mg, 11.2% yield). LC-MS: m/z 467.5 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 7.85 (s, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.78 (s, 1H), 6.65 (d, J = 7.8 Hz, 1H), 4.22 (q, J = 6.8 Hz, 2H), 4.05 - 3.90 (m, 2H),

3.85 - 3.70 (m, 5H), 2.28 - 2.19 (m, 2H), 2.06 - 2.02 (m, 2H), 1.98 (s, 3H), 1.90 - 1.78 (m, 2H), 1.62 (t, *J* = 10.8 Hz, 2H), 1.47 (t, *J* = 6.8 Hz, 3H), 1.23 - 1.13 (m, 2H), 0.38 -0.27 (m, 2H).

[0555] The compounds in Table 1 were synthesized using a similar procedure described in the Examples above using the appropriate starting materials. Separation conditions for certain compounds is as follows.

[0556] Compounds 125 and 126 were separated as follows: Prep. HPLC purification (Column: YMC-Actus Triart C18, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 60 mL/min; Gradient: 20% B to 56% B in 8 min).

[0557] Compounds 130 and 131 were separated as follows: Prep.HPLC purification (Column: XBridge Prep OBD C18 Column, 30* 150 mm, 5 μm; Mobile Phase A: Water (10 mM NH_4HCO_3), Mobile Phase B: CH3CN; Flow rate: 60 mL/min; Gradient: 5% B to 85% B in 8 min).

[0558] Compounds 158 and 159 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK AD (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1%NH_3H_2O in EtOH]; B%: 35%-35%).

[0559] Compounds 196 and 197 were separated as follows: Prep. HPLC purification (Column: Welch Xtimate C18 150 * 25 mm, 5 μm; Mobile Phase A: Water (0.05% $NH_3 \cdot H_2O$+10 mM NH_4HCO_3), Mobile Phase B: CH3CN; Flow rate: 40 mL/min; Gradient: 22% B to 55% B in 7 min).

[0560] Compounds 200 and 201 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK IG (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% $NH_3 \cdot H_2O$ in MeOH]; B%: 30%-30%).

[0561] Compounds 210 and 211 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK IG (250 mm*30 mm, 10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in EtOH]; B%: 35% - 35%).

[0562] Compounds 213 and 214 were separated as follows: Prep. HPLC purification (Column: Welch Xtimate C18 150 * 30 mm, 5 μm; Mobile Phase A: Water (0.05% $NH_3 \cdot H_2O$+10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 40 mL/min; Gradient: 22% B to 55% B in 7 min).

[0563] Compounds 216 and 217 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK AD (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in MeOH]; B%: 30%-30%).

[0564] Compounds 223 and 224 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK AD (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in MeOH]; B%: 20%-20%).

[0565] Compounds 237 and 238 were separated as follows: Prep. HPLC purification (Column: Boston Prime C18 150 * 30 mm, 5 μm; Mobile Phase A: Water (0.05% $NH_3 \cdot H_2O$+10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Flow rate: 30 mL/min; Gradient: 30% B to 60% B in 7 min).

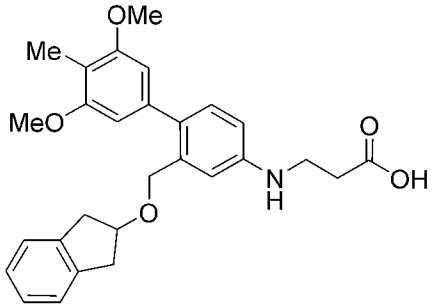
[0566] Compounds 241 and 242 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK AD (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in MeOH]; B%: 35%-35%).

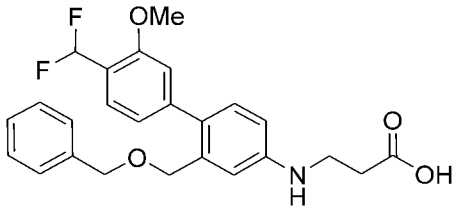
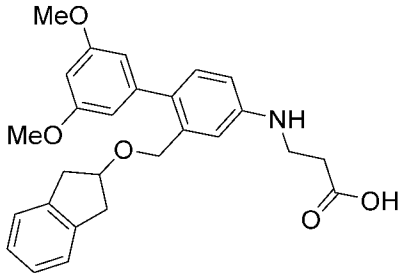
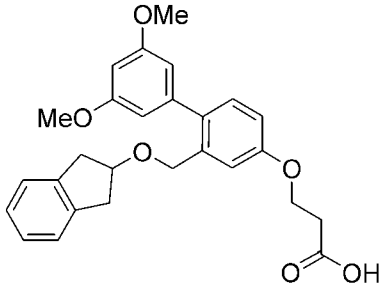
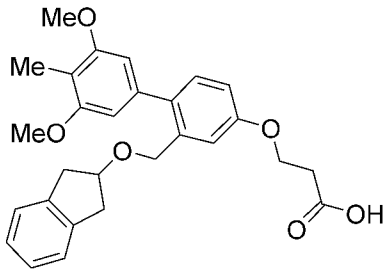
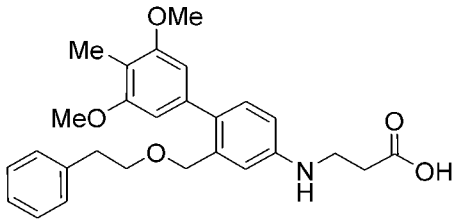
[0567] Compounds 259 and 260 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK IG (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in *i*-PrOH]; B%: 20%-20%).

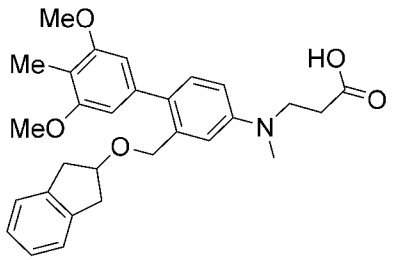
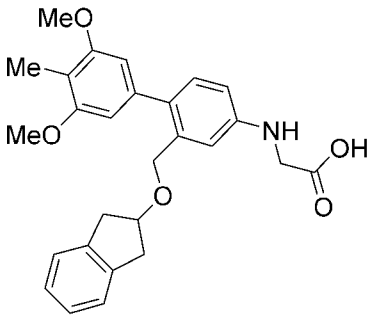
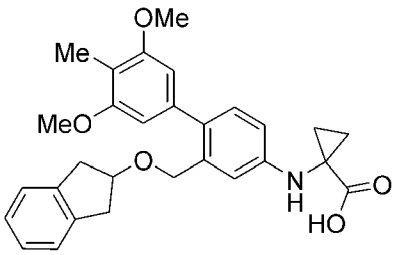
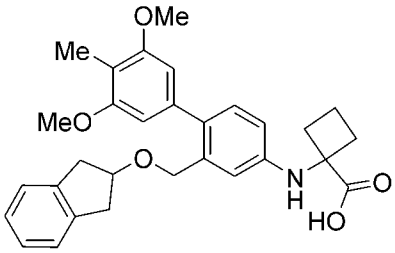
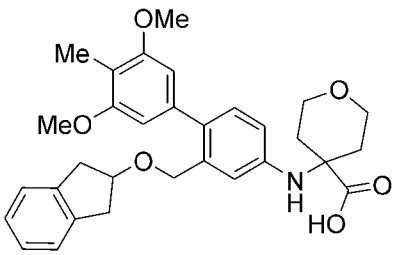
[0568] Compounds 268 and 269 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK AD (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in EtOH]; B%: 20%-20%).

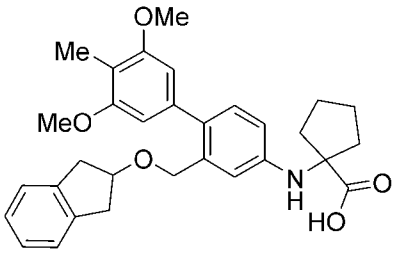
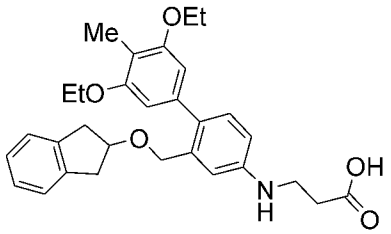
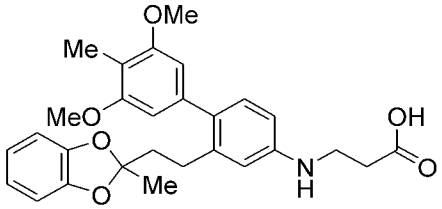
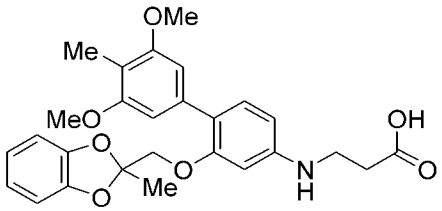
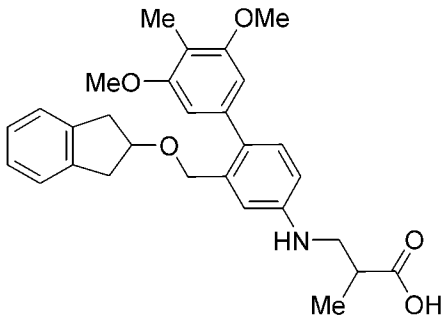
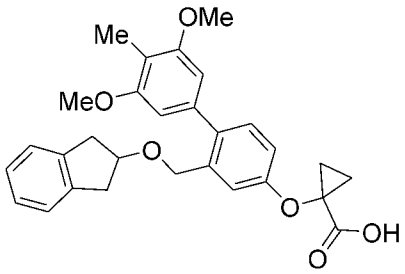
[0569] Compounds 299 and 300 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK IG (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in *i*-PrOH]; B%: 30%-30%). Flow rate: 2.5 mL/min, Column temp.: 40 °C.

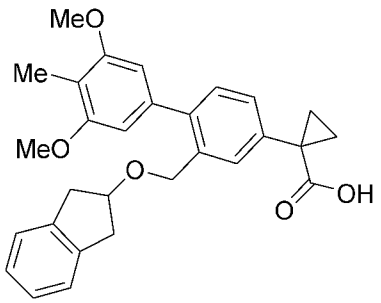
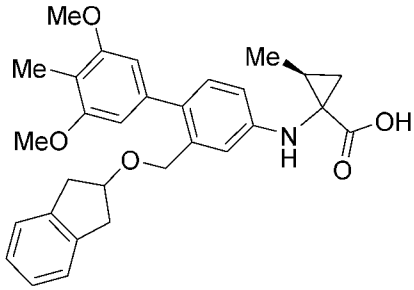
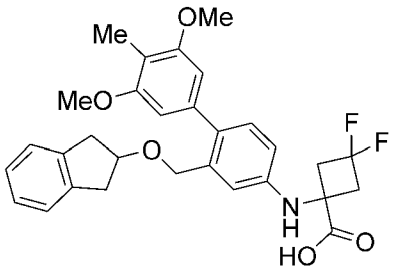
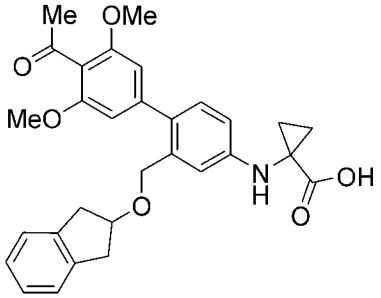
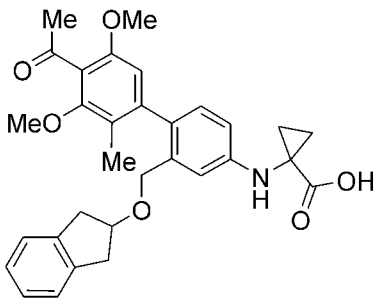
[0570] Compounds 308 and 309 were separated as follows: SFC separation (Column: DAICEL CHIRALPAK OJ (250 mm*30 mm,10 μm); mobile phase: A for CO_2, B for [0.1% NH_3H_2O in *i*-PrOH]; B%: 20%-20%). Flow rate: 2.5 mL/min, Column temp.: 40 °C.

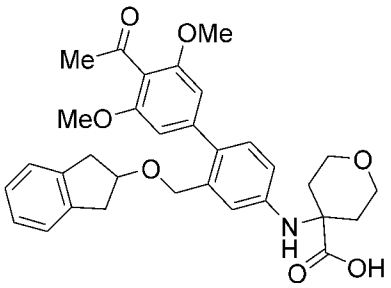
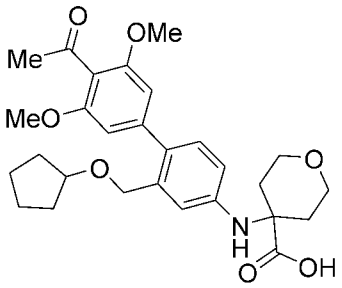
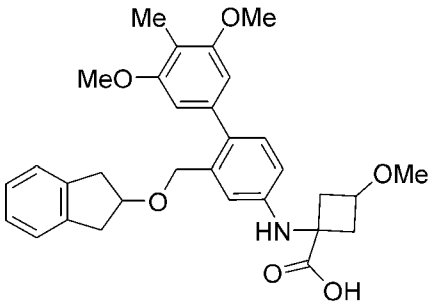
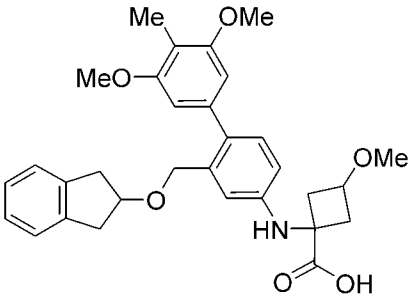
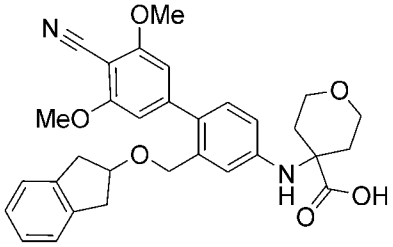
Compound	Structure	LC-MS: m/z
101		462.0 $(M+H)^+$

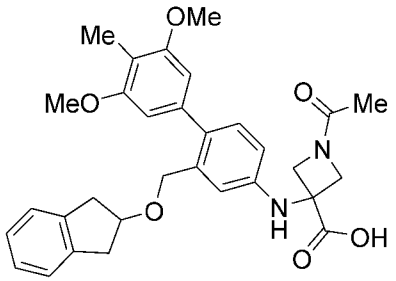
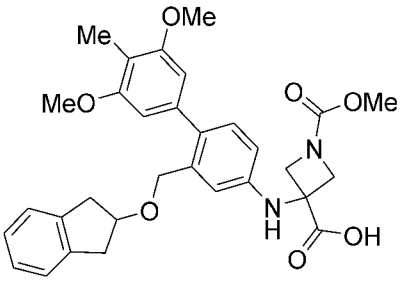
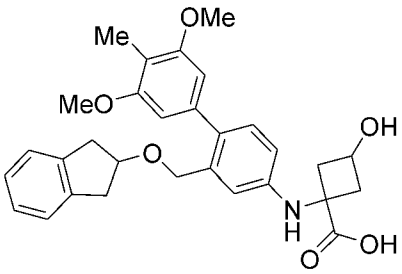
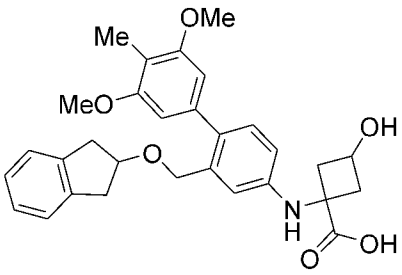
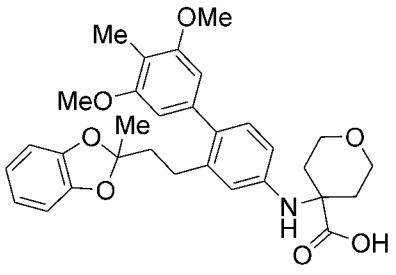
Compound	Structure	LC-MS: m/z
102		442.0 $(M+H)^+$
103		448.4 $(M+H)^+$
104		449.2 $(M+H)^+$
105		485.3 $(M+Na)^+$
106		450.2 $(M+H)^+$

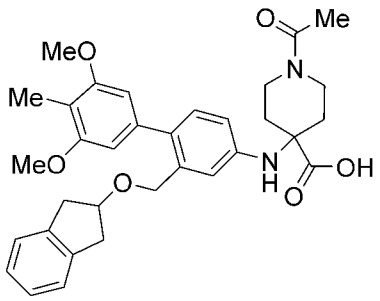
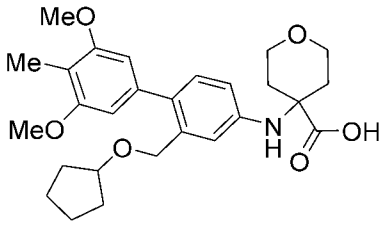
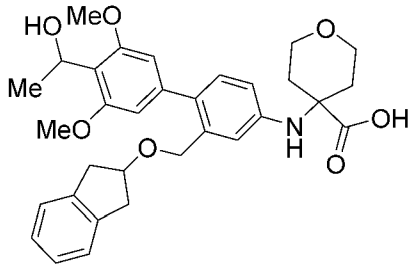
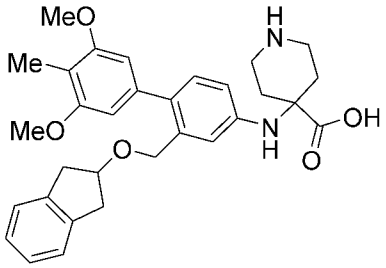
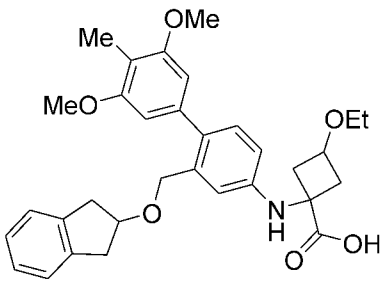
Compound	Structure	LC-MS: m/z
107		476.2 $(M+H)^+$
108		448.2 $(M+H)^+$
109		496.2 $(M+Na)^+$
110		488.2 $(M+H)^+$
111		518.4 $(M+H)^+$

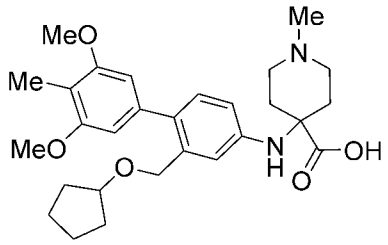
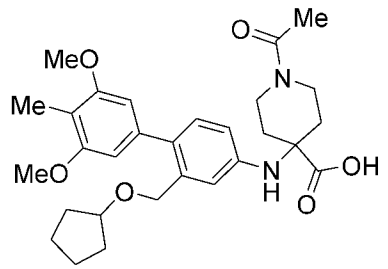
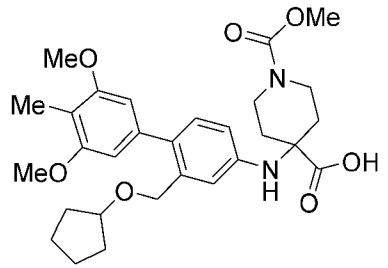
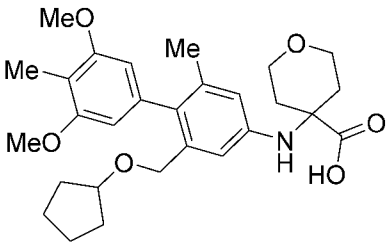
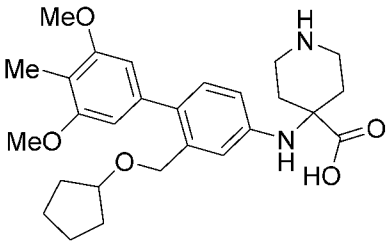
Compound	Structure	LC-MS: m/z
112		502.2 $(M+H)^+$
113		490.2 $(M+H)^+$
114		478.3 $(M+H)^+$
115		480.2 $(M+H)^+$
116		476.2 $(M+H)^+$
117		497.2 $(M+Na)^+$

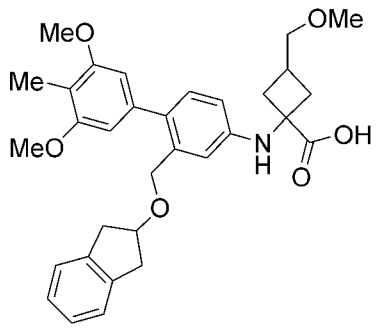
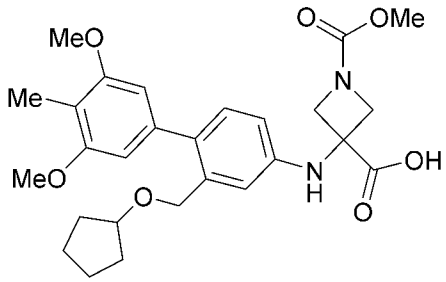
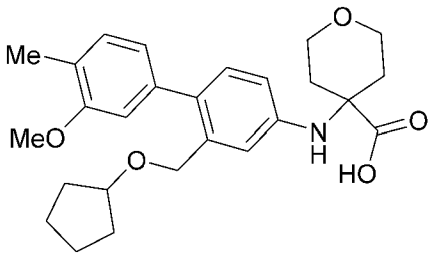
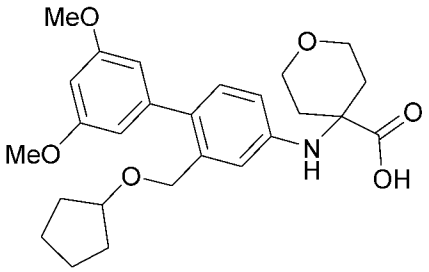
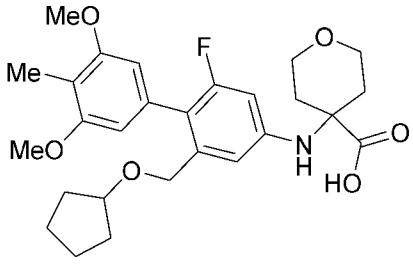
Compound	Structure	LC-MS: m/z
118		457.0 $(M-H)^-$
119		488.2 $(M+H)^+$
120		524.3 $(M+H)^+$
121		502.2 $(M+H)^+$
122		516.4 $(M+H)^+$

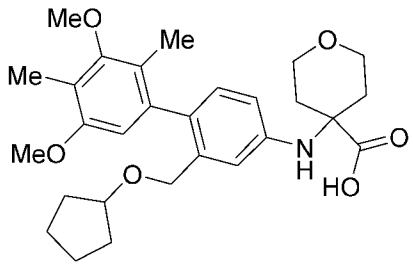
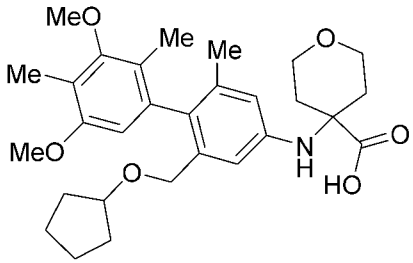
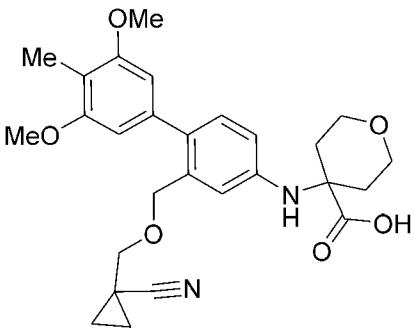
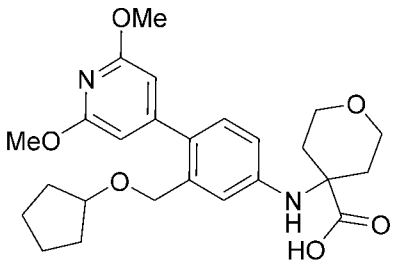
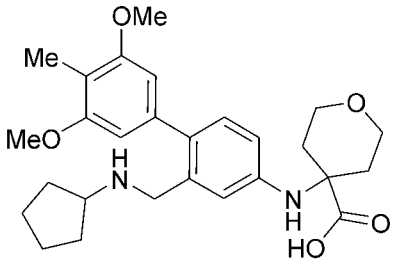
Compound	Structure	LC-MS: m/z
123		546.4 $(M+H)^+$
124		498.2 $(M+H)^+$
125	 Enantiomer 1	518.3 $(M+H)^+$
126	 Enantiomer 2	518.2 $(M+H)^+$
127		529.2 $(M+H)^+$

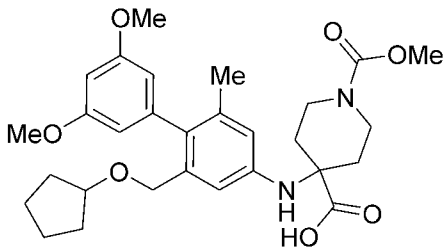
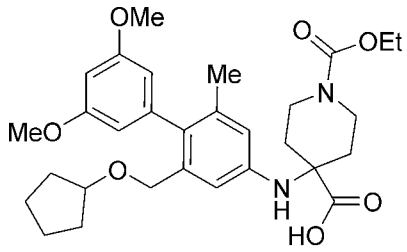
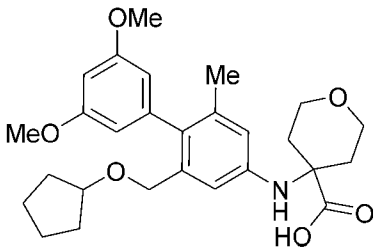
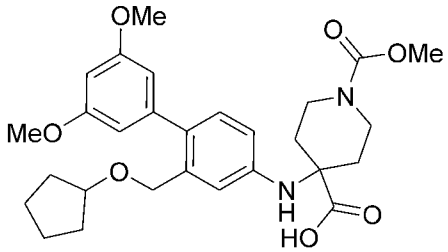
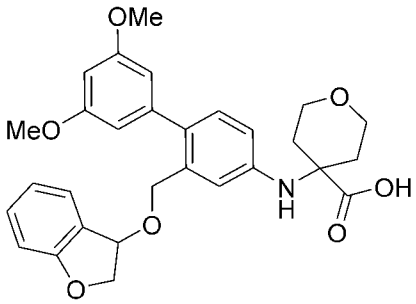
Compound	Structure	LC-MS: m/z
128		531.2 $(M+H)^+$
129		547.3 $(M+H)^+$
130	 Enantiomer 1	504.1 $(M+H)^+$
131	 Enantiomer 2	504.1 $(M+H)^+$
132		534.1 $(M+H)^+$

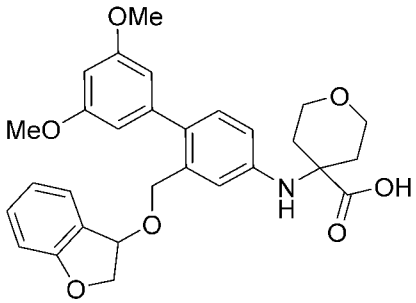
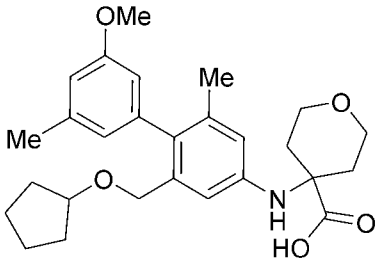
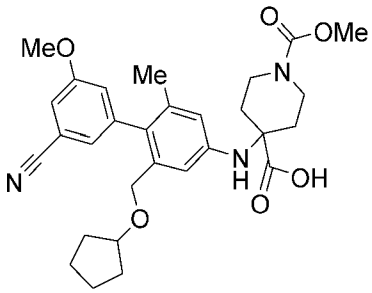
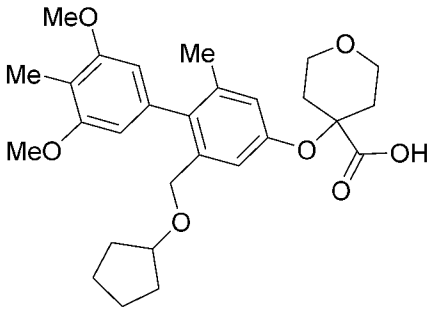
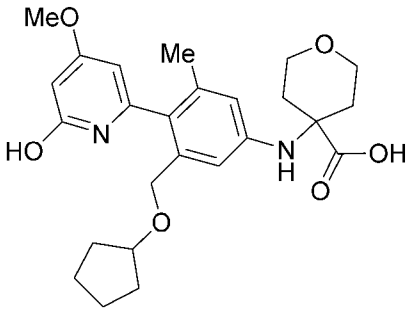
Compound	Structure	LC-MS: m/z
133		559.1 $(M+H)^+$
134		470.2 $(M+H)^+$
135		548.3 $(M+H)^+$
136		517.3 $(M+H)^+$
137		532.1 $(M+H)^+$

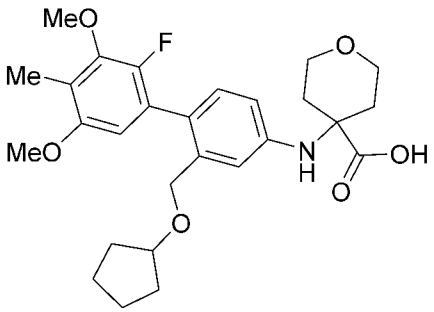
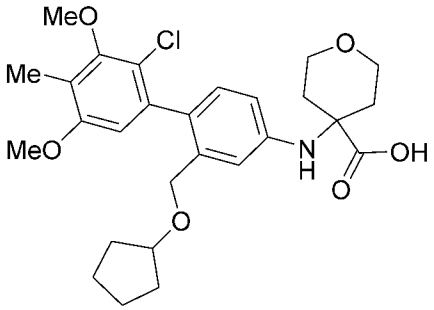
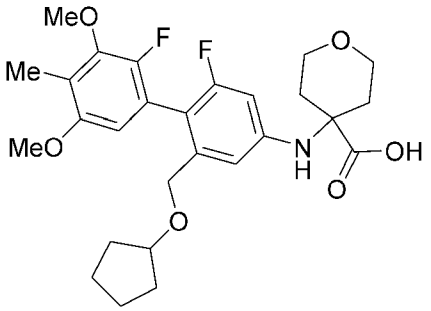
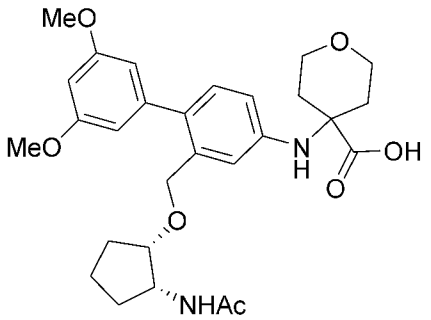
Compound	Structure	LC-MS: m/z
138		483.2 $(M+H)^+$
139		511.3 $(M+H)^+$
140		527.2 $(M+H)^+$
141		484.1 $(M+H)^+$
142		469.1 $(M+H)^+$

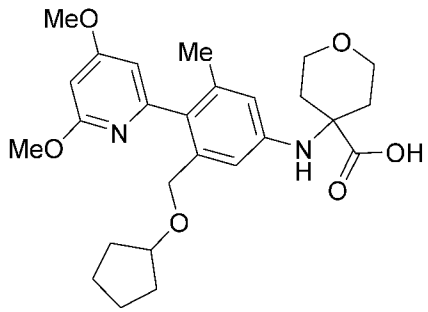
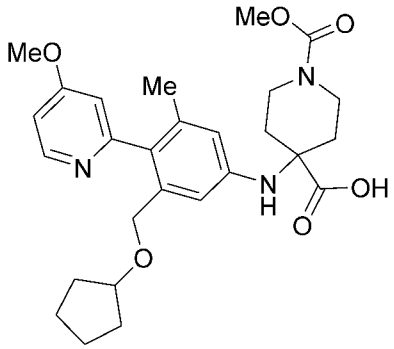
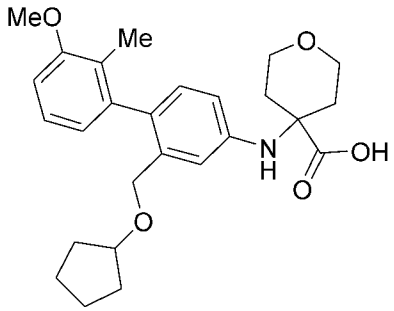
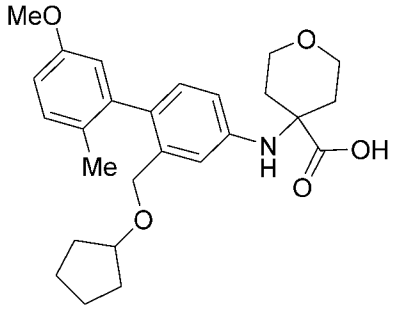
Compound	Structure	LC-MS: m/z
143		532.4 $(M+H)^+$
144		499.1 $(M+H)^+$
145		440.1 $(M+H)^+$
146		456.1 $(M+H)^+$
147		488.4 $(M+H)^+$

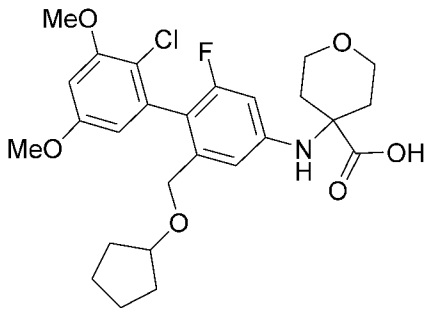
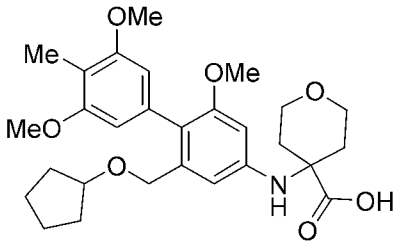
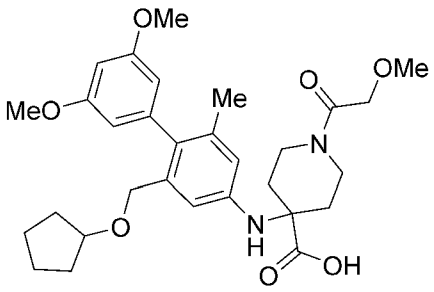
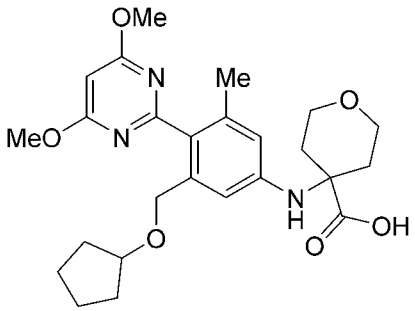
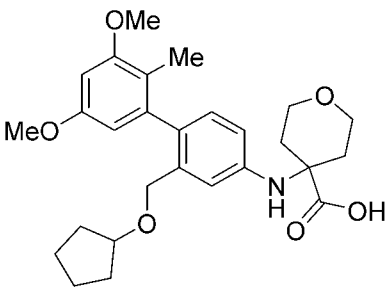
Compound	Structure	LC-MS: m/z
148		484.2 $(M+H)^+$
149		498.2 $(M+H)^+$
151		481.1 $(M+H)^+$
152		457.1 $(M+H)^+$
153		469.2 $(M+H)^+$

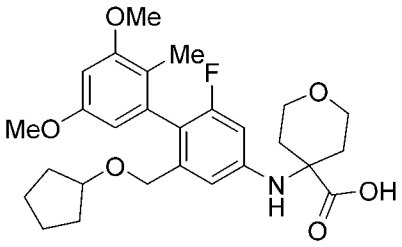
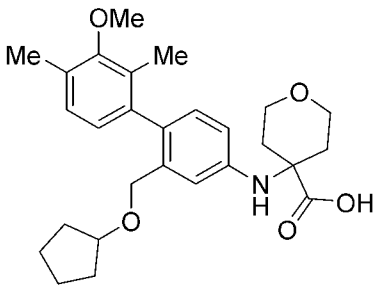
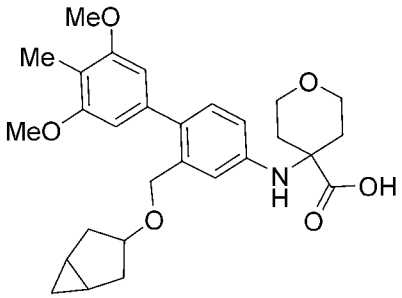
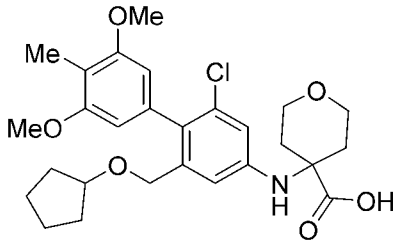
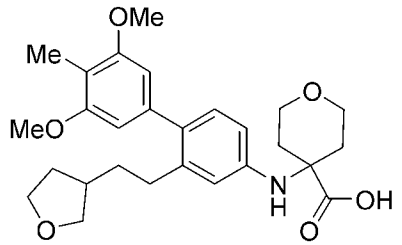
Compound	Structure	LC-MS: m/z
154		549.4 $(M+Na)^+$
155		541.4 $(M+H)^+$
156		470.1 $(M+H)^+$
157		535.4 $(M+Na)^+$
158	 Enantiomer 1	506.0 $(M+H)^+$

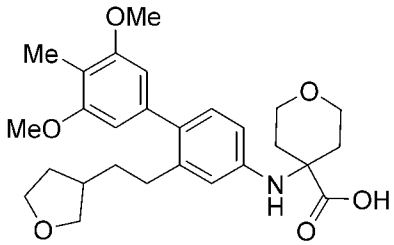
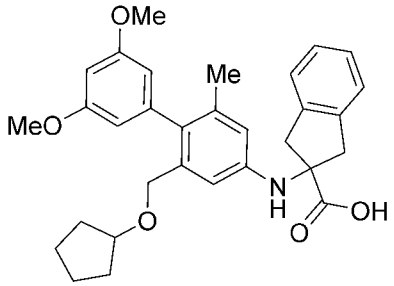
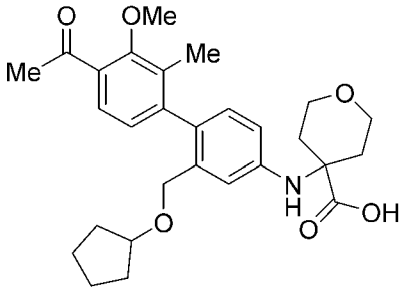
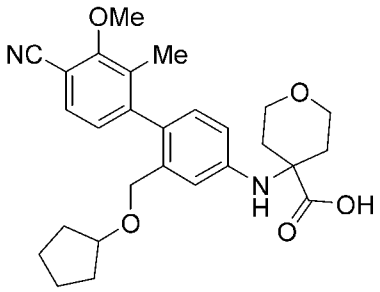
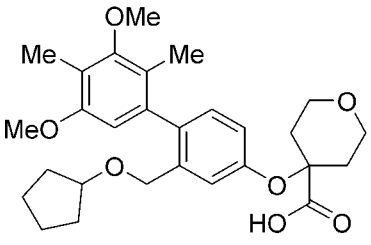
Compound	Structure	LC-MS: m/z
159	 Enantiomer 2	506.0 $(M+H)^+$
160		454.2 $(M+H)^+$
161		522.2 $(M+H)^+$
163		507.4 $(M+Na)^+$
164		457.1 $(M+H)^+$

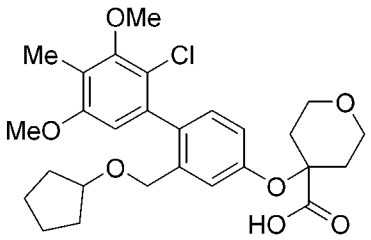
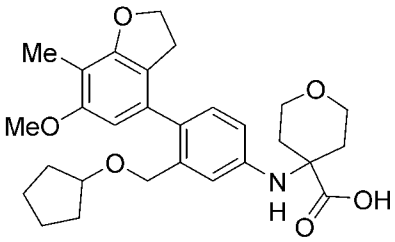
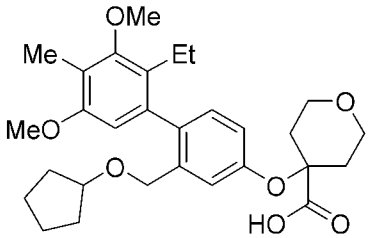
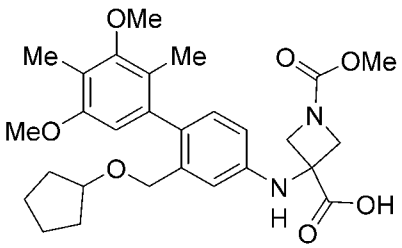
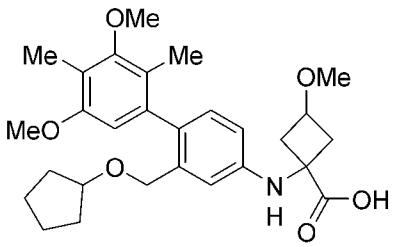
Compound	Structure	LC-MS: m/z
165		488.1 $(M+H)^+$
166		504.0 $(M+H)^+$
168		506.4 $(M+H)^+$
169		513.4 $(M+H)^+$

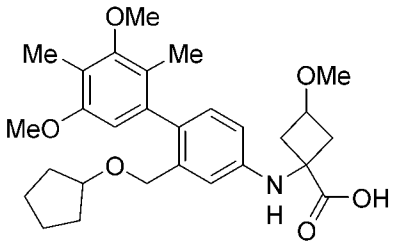
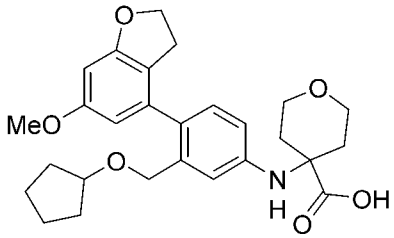
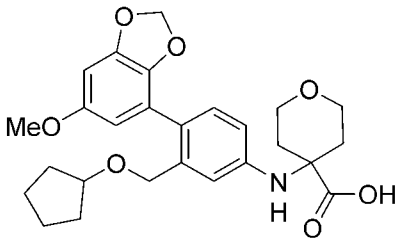
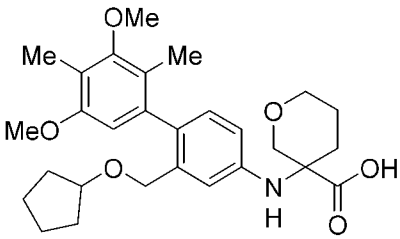
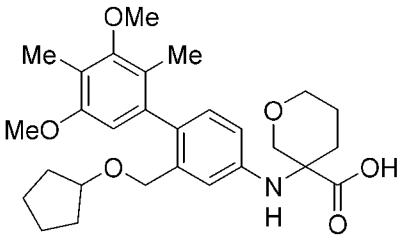
Compound	Structure	LC-MS: m/z
170		471.2 $(M+H)^+$
171		498.4 $(M+H)^+$
172		440.0 $(M+H)^+$
173		440.0 $(M+H)^+$

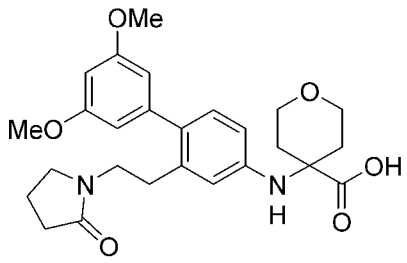
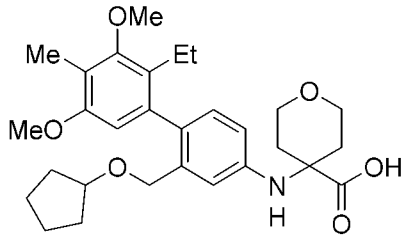
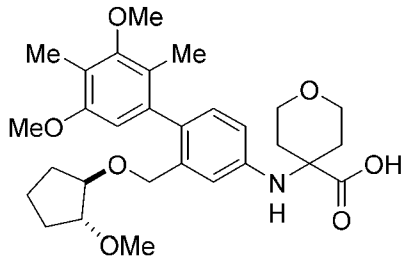
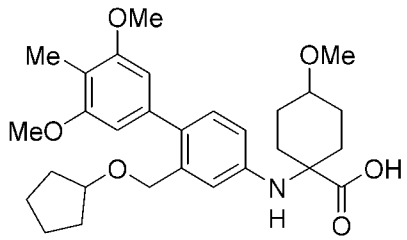
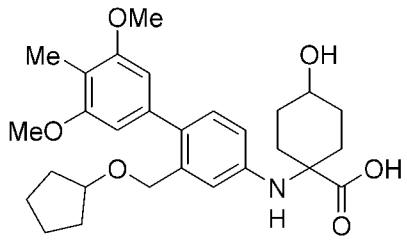
Compound	Structure	LC-MS: m/z
174		508.1 $(M+H)^+$
175		500.4 $(M+H)^+$
176		563.3 $(M+Na)^+$
178		472.0 $(M+H)^+$
179		470.0 $(M+H)^+$

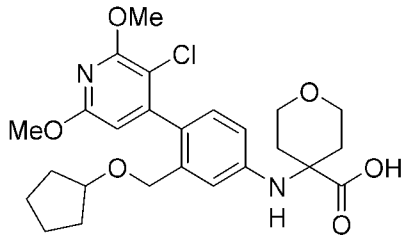
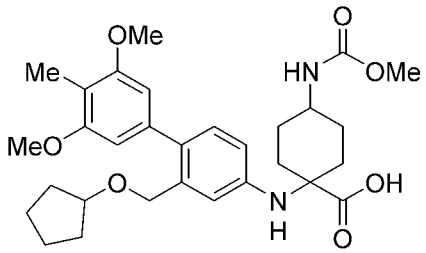
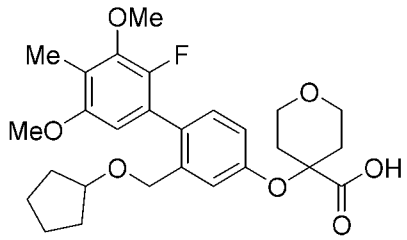
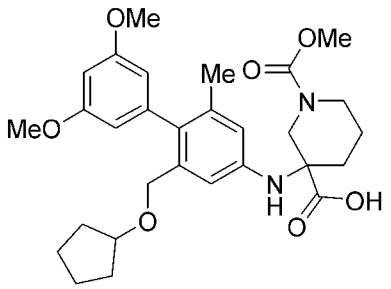
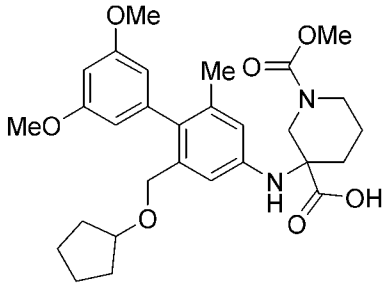
Compound	Structure	LC-MS: m/z
180		488.3 $(M+H)^+$
181		454.1 $(M+H)^+$
182		482.1 $(M+H)^+$
184		504.3 $(M+H)^+$
185	 Enantiomer 1	470.3 $(M+H)^+$

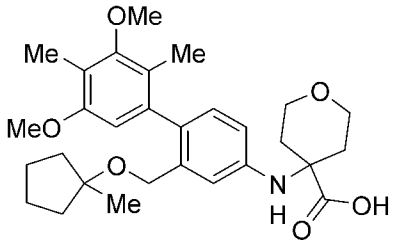
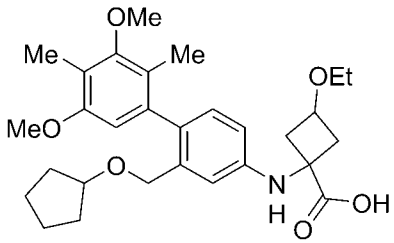
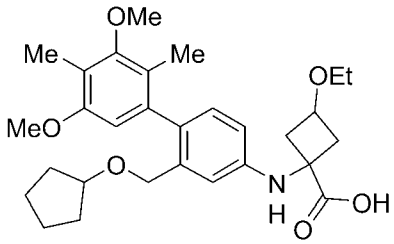
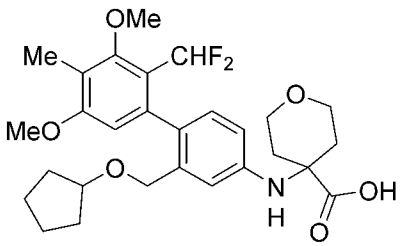
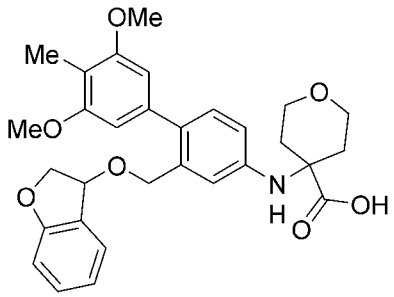
Compound	Structure	LC-MS: m/z
186	 Enantiomer 2	470.3 $(M+H)^+$
188		502.3 $(M+H)^+$
189		482.1 $(M+H)^+$
190		465.3 $(M+H)^+$
191		507.2 $(M+Na)^+$

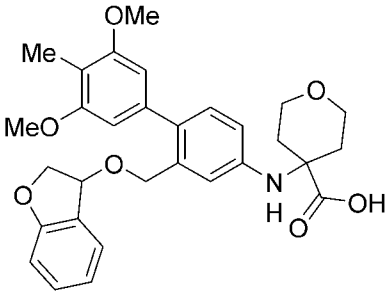
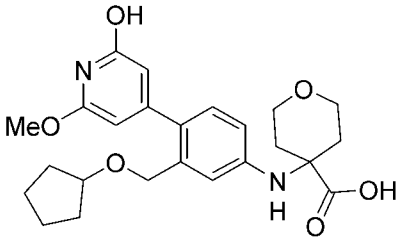
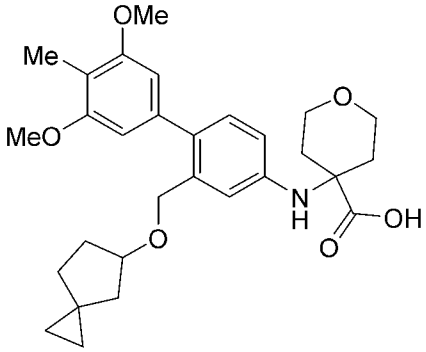
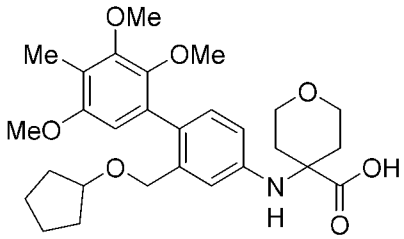
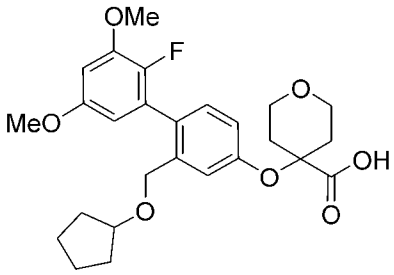
Compound	Structure	LC-MS: m/z
192		522.2 $(M+NH_4)^+$
193		482.3 $(M+H)^+$
194		521.3 $(M+Na)^+$
195		535.1 $(M+Na)^+$
196	 Enantiomer 1	484.3 $(M+H)^+$

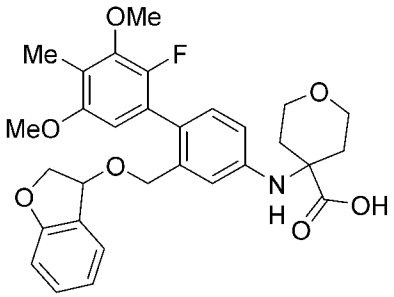
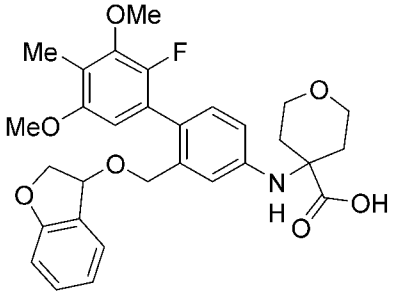
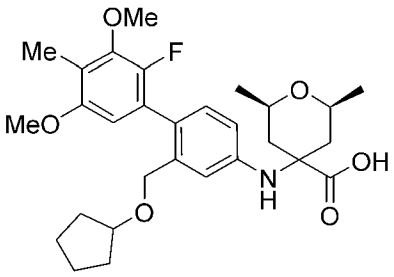
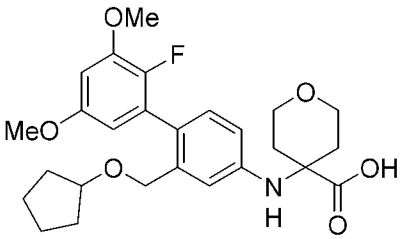
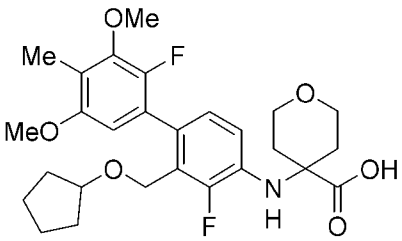
Compound	Structure	LC-MS: m/z
197	 Enantiomer 2	484.3 $(M+H)^+$
198		468.3 $(M+H)^+$
199		470.3 $(M+H)^+$
200	 Enantiomer 1	484.3 $(M+H)^+$
201	 Enantiomer 2	484.3 $(M+H)^+$

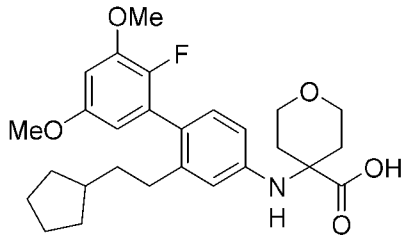
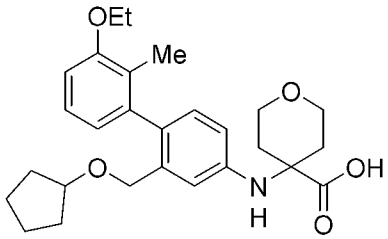
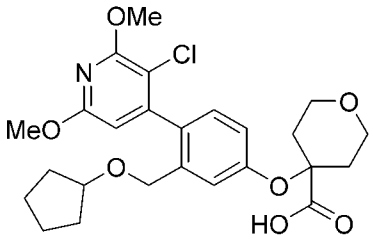
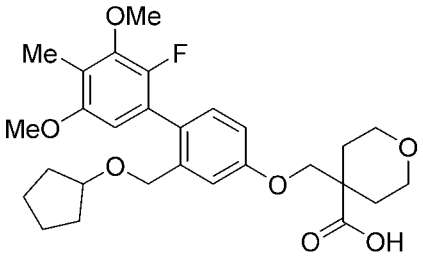
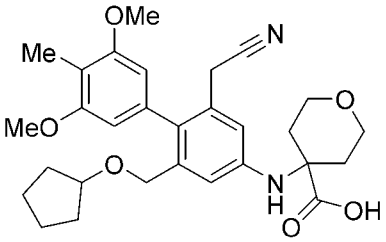
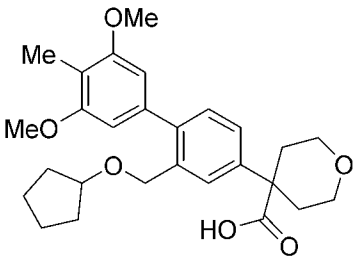
Compound	Structure	LC-MS: m/z
202		469.0 $(M+H)^+$
203		498.3 $(M+H)^+$
204	 Trans (mixture of enantiomers)	514.3 $(M+H)^+$
205		498.1 $(M+H)^+$
206		484.1 $(M+H)^+$

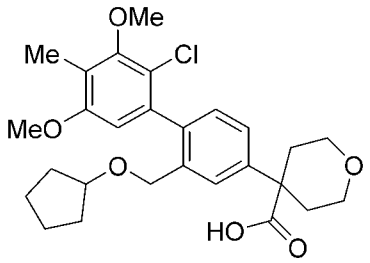
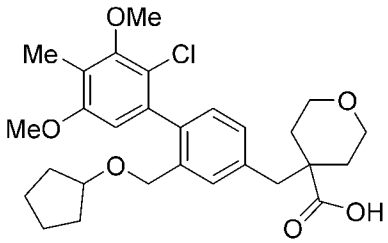
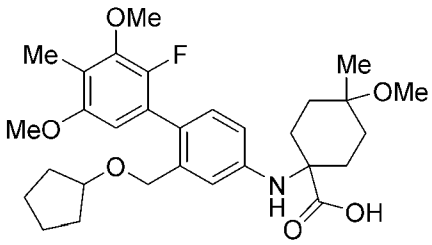
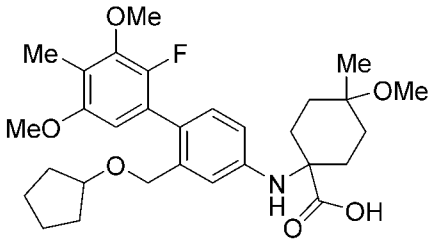
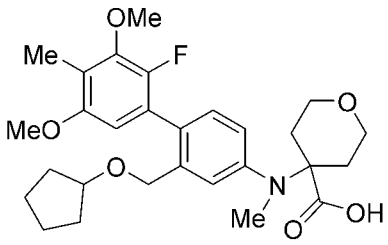
Compound	Structure	LC-MS: m/z
207		491.2 $(M+H)^+$
208		541.2 $(M+H)^+$
209		506.3 $(M+NH_4)^+$
210	 Enantiomer 1	527.2 $(M+H)^+$
211	 Enantiomer 2	527.2 $(M+H)^+$

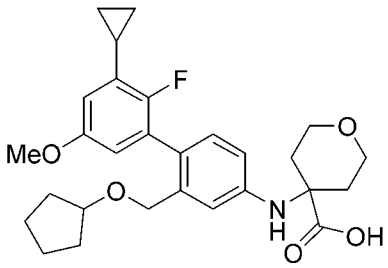
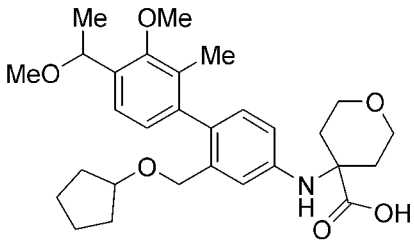
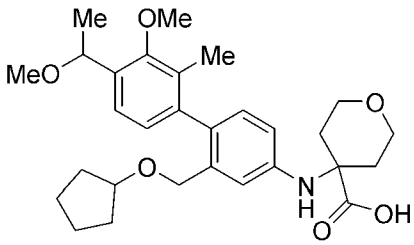
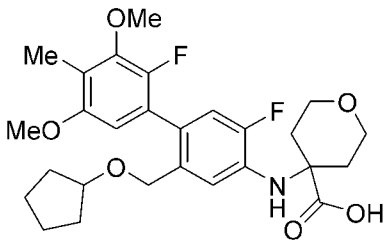
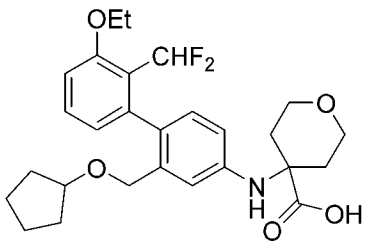
Compound	Structure	LC-MS: m/z
212		498.4 $(M+H)^+$
213	 Enantiomer 1	498.1 $(M+H)^+$
214	 Enantiomer 2	498.2 $(M+H)^+$
215		520.1 $(M+H)^+$
216	 Enantiomer 1	520.4 $(M+H)^+$

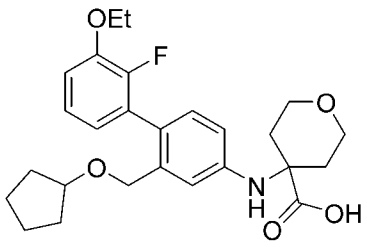
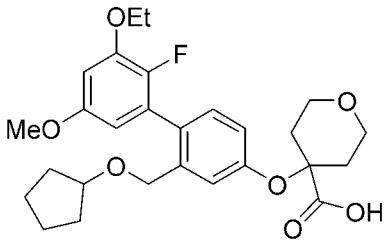
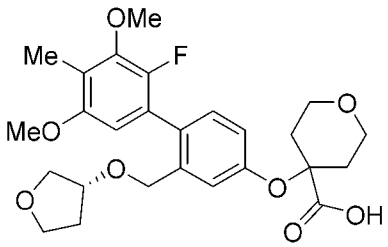
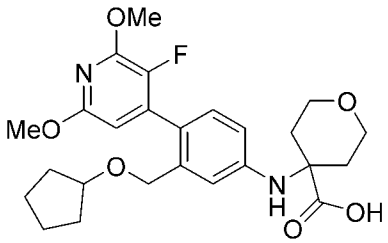
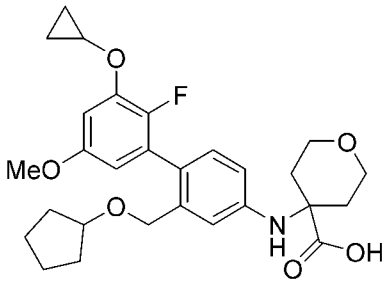
Compound	Structure	LC-MS: m/z
217	 Enantiomer 2	520.4 $(M+H)^+$
218		443.0 $(M+H)^+$
219		496.1 $(M+H)^+$
220		500.4 $(M+H)^+$
222		492.2 $(M+NH_4)^+$

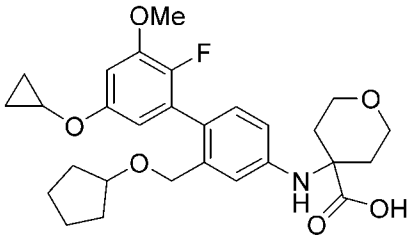
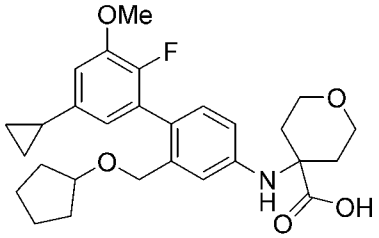
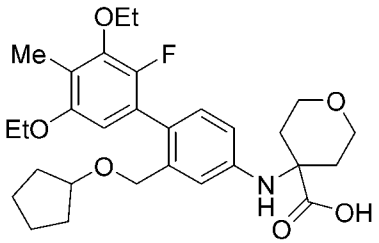
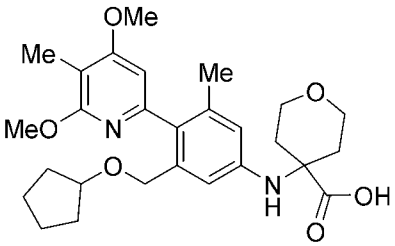
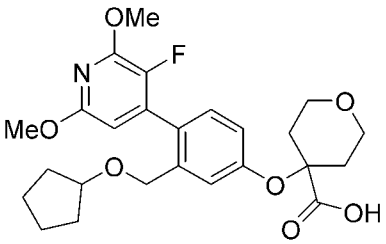
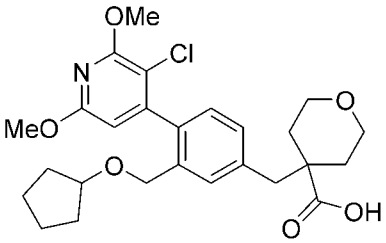
Compound	Structure	LC-MS: m/z
223	 Enantiomer 1	538.3 $(M+H)^+$
224	 Enantiomer 2	538.3 $(M+H)^+$
225		516.4 $(M+H)^+$
226		474.0 $(M+H)^+$
227		528.1 $(M+Na)^+$

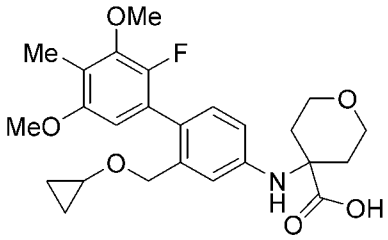
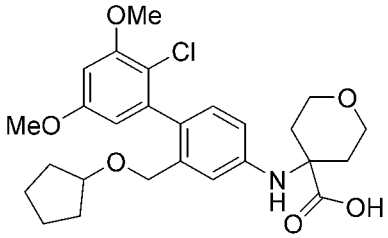
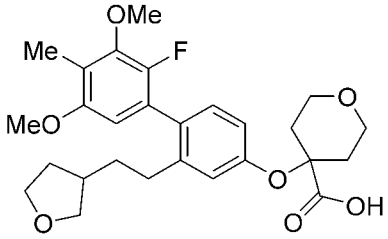
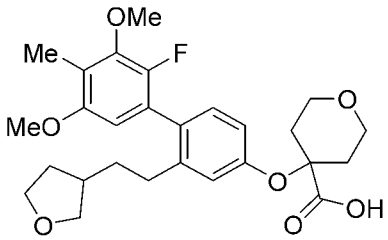
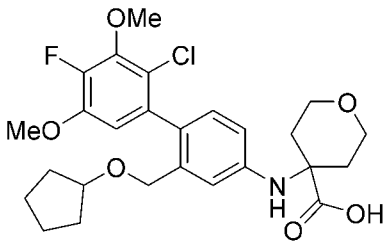
Compound	Structure	LC-MS: m/z
228		472.3 $(M+H)^+$
229		454.1 $(M+H)^+$
230		492.0 $(M+H)^+$
232		520.3 $(M+NH_4)^+$
233		509.1 $(M+H)^+$
234		477.3 $(M+Na)^+$

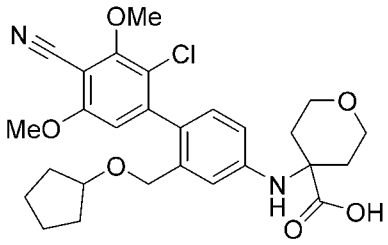
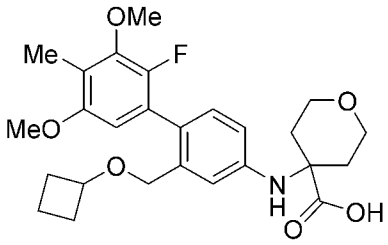
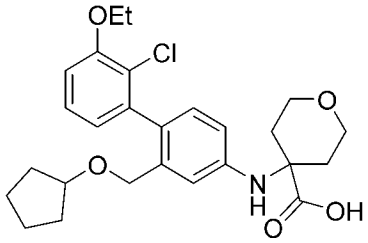
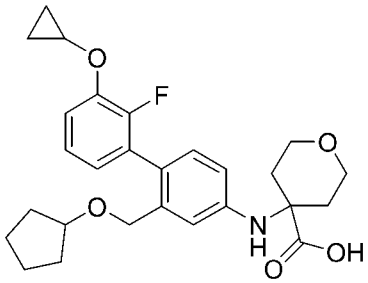
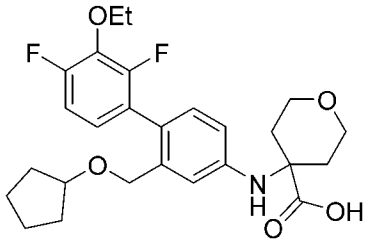
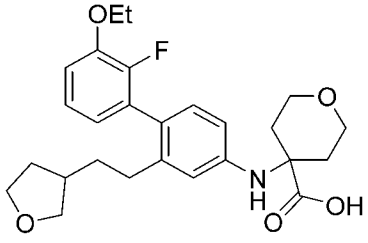
Compound	Structure	LC-MS: m/z
235		506.2 $(M+NH_4)^+$
236		525.1 $(M+Na)^+$
237	 Enantiomer 1	530.4 $(M+H)^+$
238	 Enantiomer 2	530.4 $(M+H)^+$
239		502.3 $(M+H)^+$

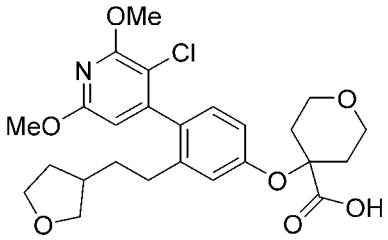
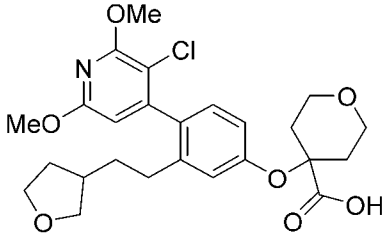
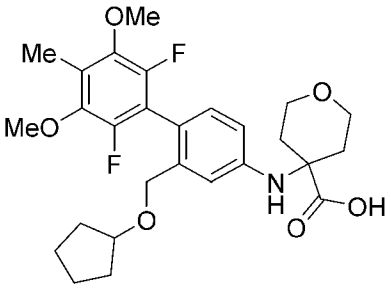
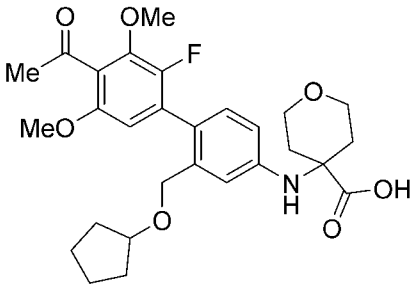
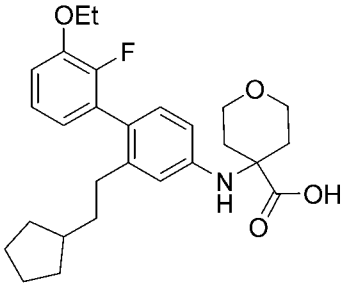
Compound	Structure	LC-MS: m/z
240		484.0 $(M+H)^+$
241	 Enantiomer 1	498.2 $(M+H)^+$
242	 Enantiomer 2	498.1 $(M+H)^+$
243		506.0 $(M+H)^+$
244		490.2 $(M+NH_4)^+$

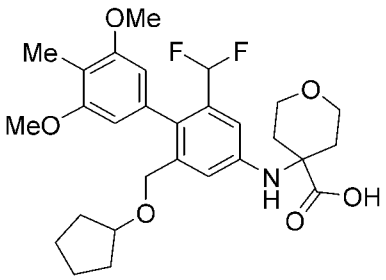
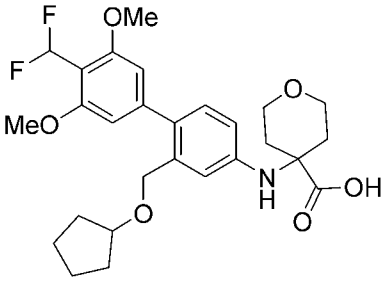
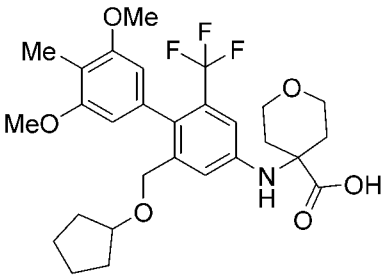
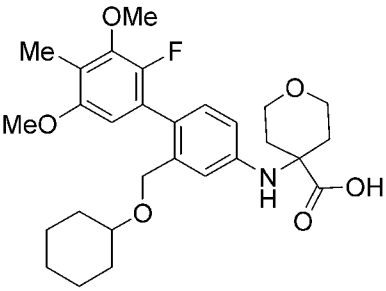
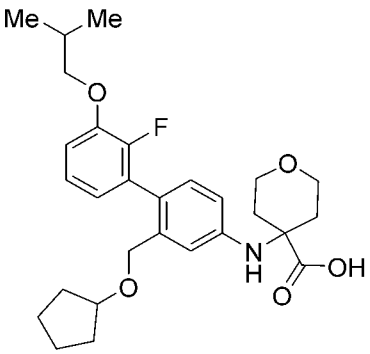
Compound	Structure	LC-MS: m/z
245		458.5 $(M+NH_4)^+$
246		511.1 $(M+Na)^+$
247		508.2 $(M+NH_4)^+$
248		475.3 $(M+H)^+$
249		500.1 $(M+H)^+$

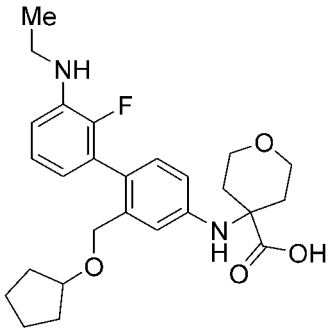
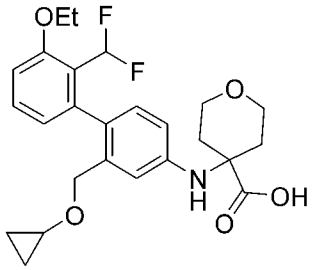
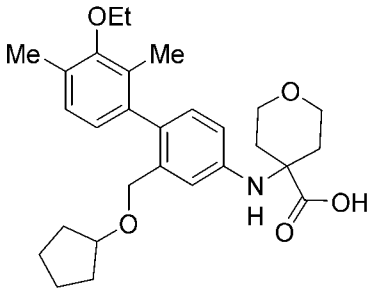
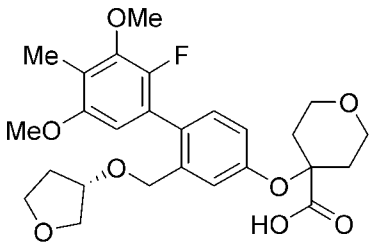
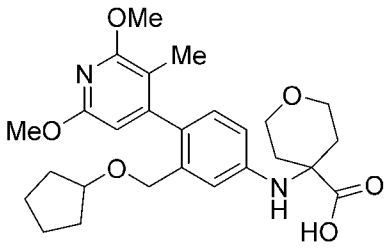
Compound	Structure	LC-MS: m/z
250		500.1 $(M+H)^+$
251		484.1 $(M+H)^+$
252		516.2 $(M+H)^+$
253		485.3 $(M+H)^+$
254		476.1 $(M+H)^+$
255		490.0 $(M+H)^+$

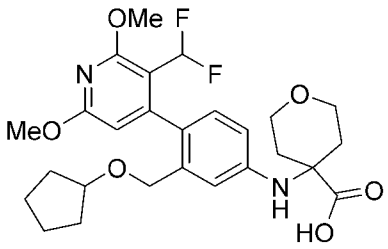
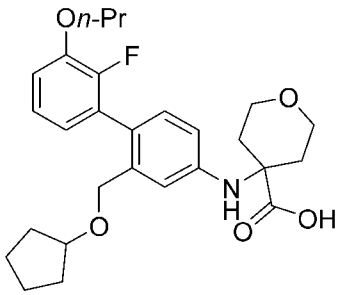
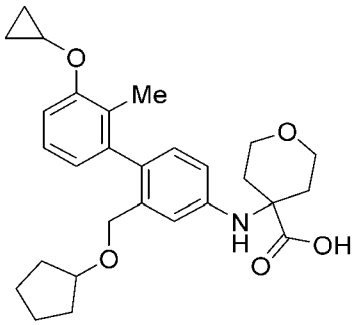
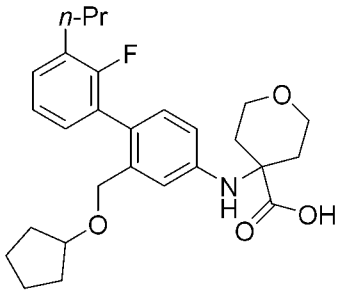
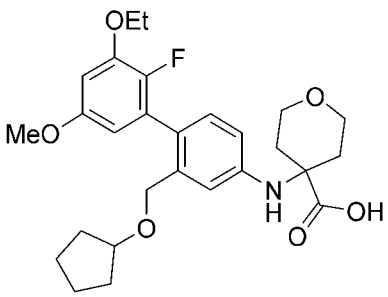
Compound	Structure	LC-MS: m/z
256		460.3 $(M+H)^+$
257		490.1 $(M+H)^+$
259 Enantiomer 1		511.2 $(M+Na)^+$
260 Enantiomer 2		511.2 $(M+Na)^+$
261		508.3 $(M+H)^+$

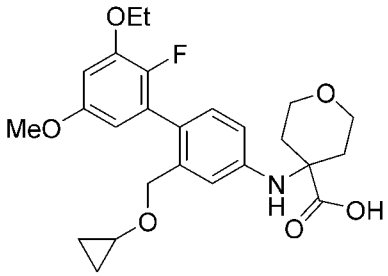
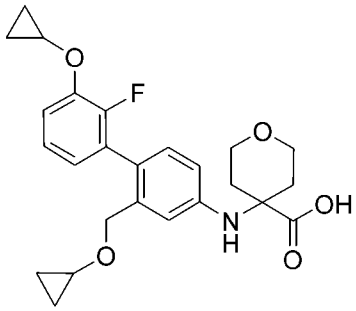
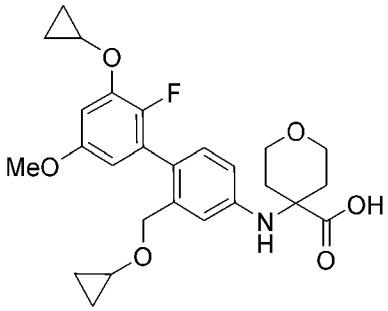
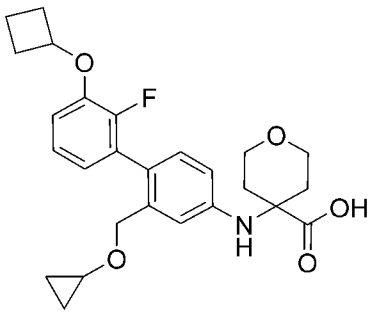
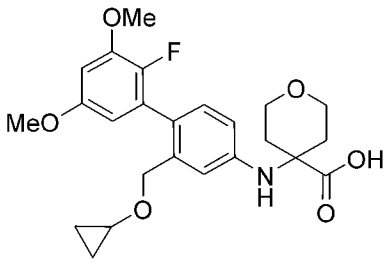
Compound	Structure	LC-MS: m/z
262		515.0 $(M+H)^+$
263		474.0 $(M+H)^+$
264		474.0 $(M+H)^+$
265		470.3 $(M+H)^+$
266		476.3 $(M+H)^+$
267		458.0 $(M+H)^+$

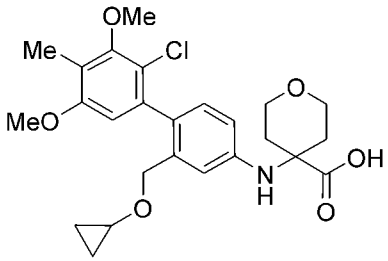
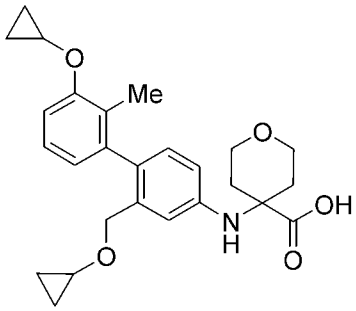
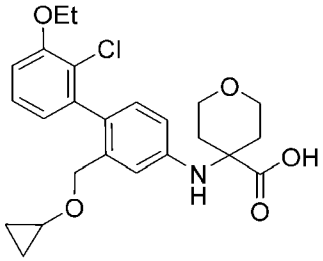
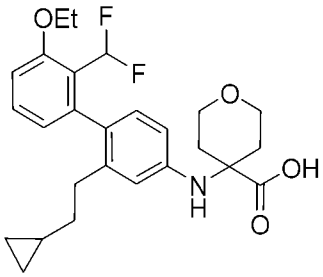
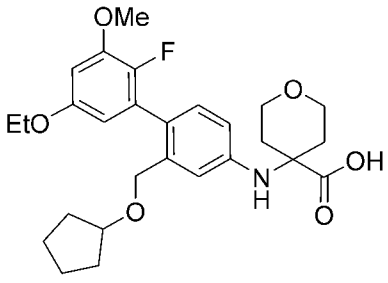
Compound	Structure	LC-MS: m/z
268	 Enantiomer 1	492.1 $(M+H)^+$
269	 Enantiomer 2	492.1 $(M+H)^+$
270		506.2 $(M+H)^+$
271		516.2 $(M+H)^+$
272		456.3 $(M+H)^+$

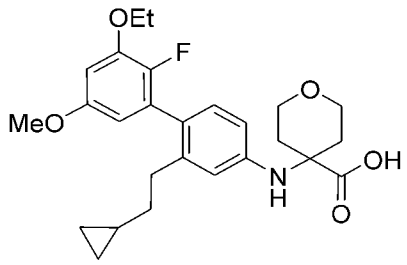
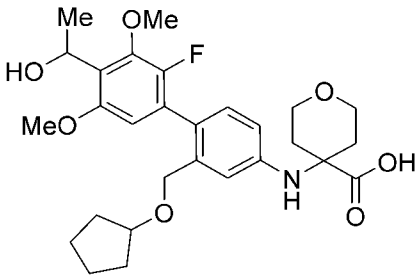
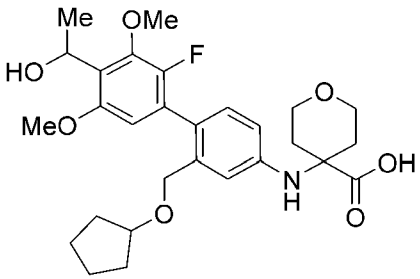
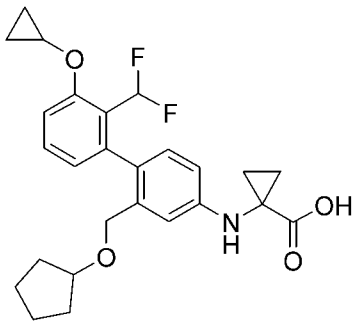
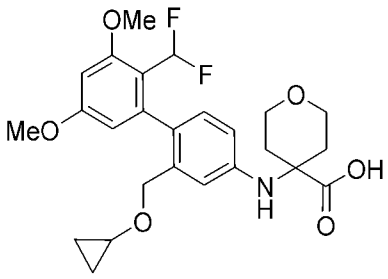
Compound	Structure	LC-MS: m/z
273		520.5 $(M+H)^+$
274		506.1 $(M+H)^+$
275		538.1 $(M+H)^+$
276		502.1 $(M+H)^+$
277		486.1 $(M+H)^+$

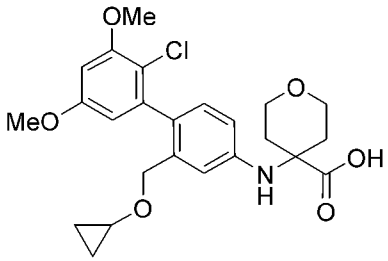
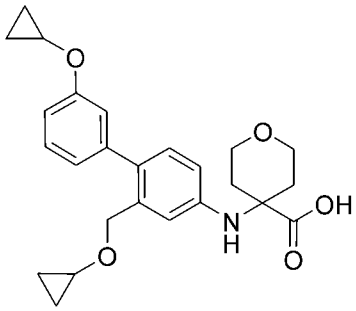
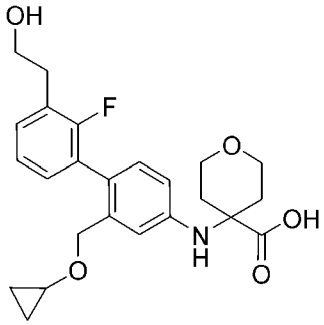
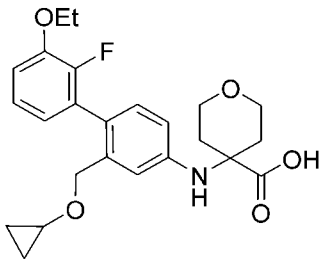
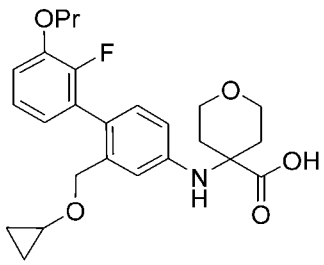
Compound	Structure	LC-MS: m/z
278		457.3 $(M+H)^+$
279		462.2 $(M+H)^+$
280		468.3$(M+H)^+$
281		508.1$(M+NH_4)^+$
282		471.3 $(M+H)^+$

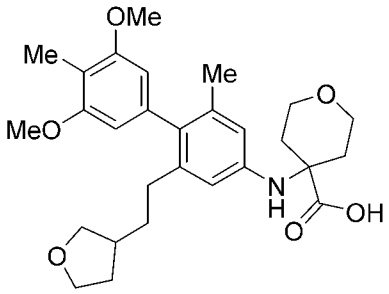
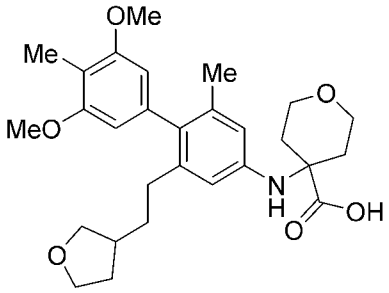
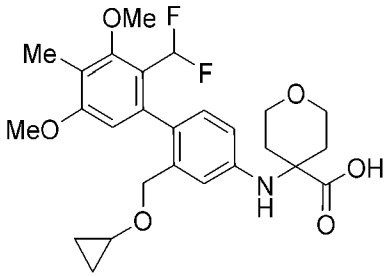
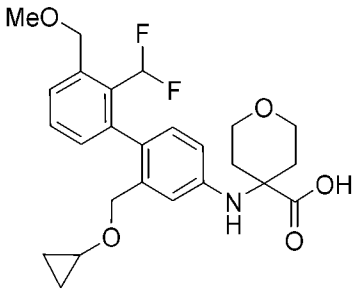
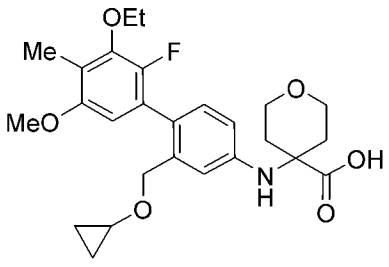
Compound	Structure	LC-MS: m/z
283		507.3 $(M+H)^+$
284		472.0 $(M+H)^+$
285		466.1 $(M+H)^+$
286		456.1 $(M+H)^+$
287		486.5 $(M-H)^-$

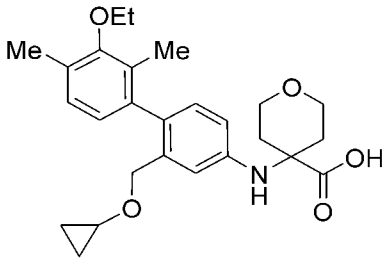
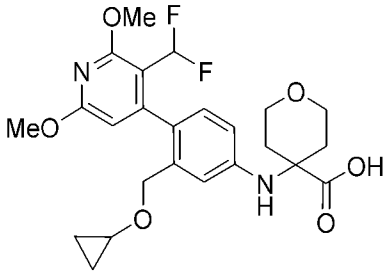
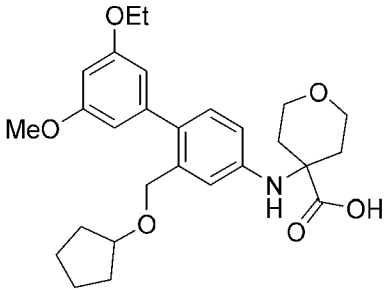
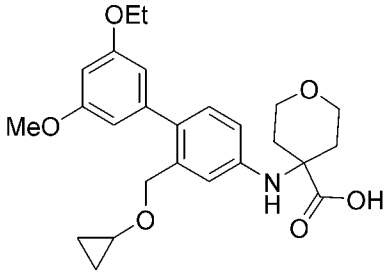
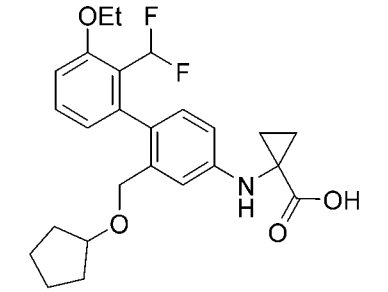
Compound	Structure	LC-MS: m/z
288		458.4 $(M-H)^-$
289		442.2 $(M+H)^+$
290		472.0 $(M+H)^+$
291		456.2 $(M+H)^+$
292		446.1 $(M+H)^+$

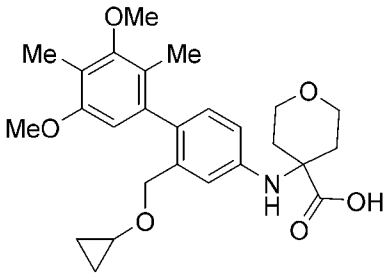
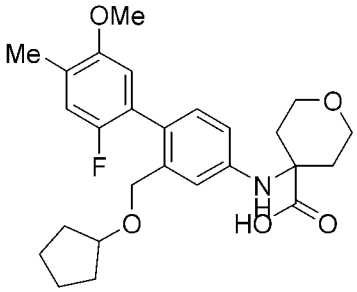
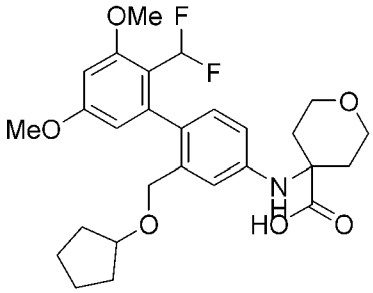
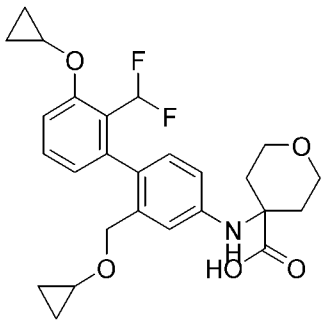
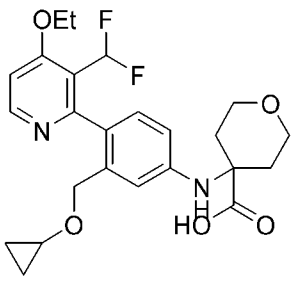
Compound	Structure	LC-MS: m/z
293		476.2 $(M+H)^+$
294		438.2 $(M+H)^+$
295		446.2 $(M+H)^+$
296		460.1 $(M+H)^+$
297		488.1 $(M+H)^+$

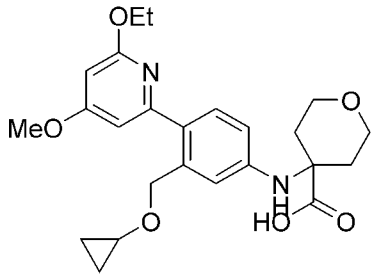
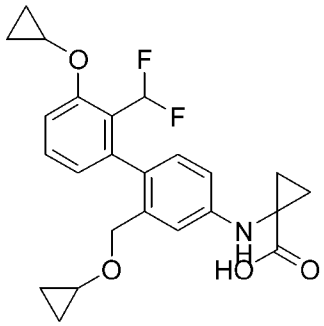
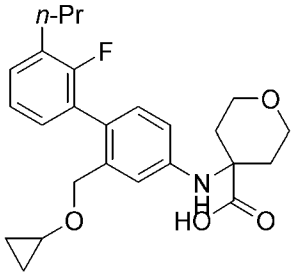
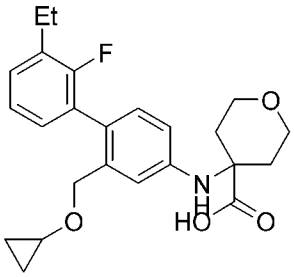
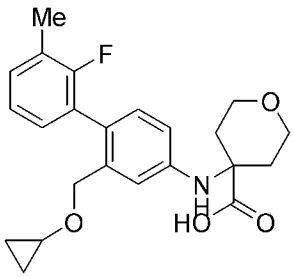
Compound	Structure	LC-MS: m/z
298		458.2 $(M+H)^+$
299	 Enantiomer 1	518.1 $(M+H)^+$
300	 Enantiomer 2	518.2 $(M+H)^+$
301		480.1 $(M+Na)^+$
302		478.2 $(M+H)^+$

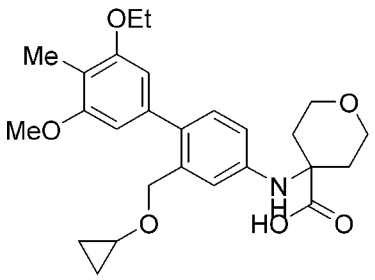
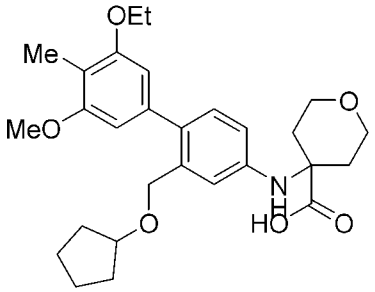
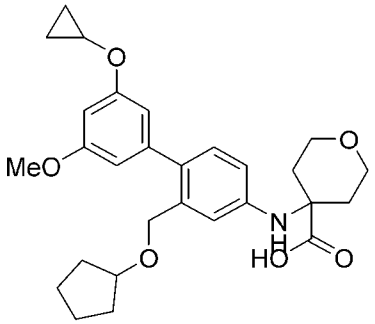
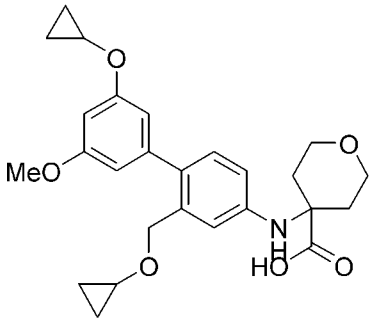
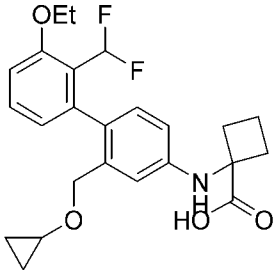
Compound	Structure	LC-MS: m/z
303		462.2 $(M+H)^+$
304		424.2 $(M+H)^+$
305		430.1 $(M+H)^+$
306		430.1 $(M+H)^+$
307		444.1 $(M+H)^+$

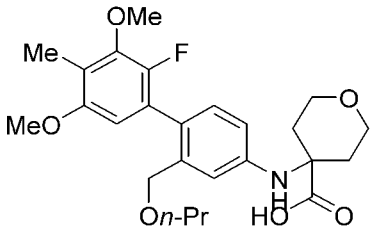
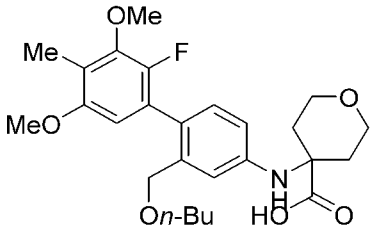
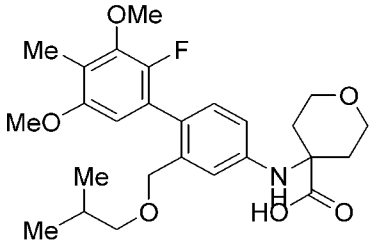
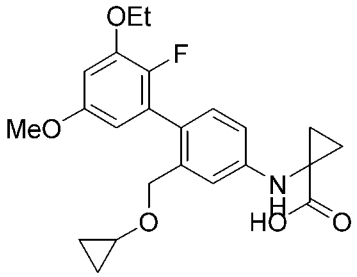
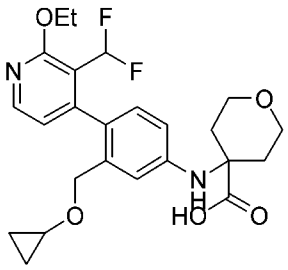
Compound	Structure	LC-MS: m/z
308	 Enantiomer 1	484.1 $(M+H)^+$
309	 Enantiomer 2	484.1 $(M+H)^+$
310		492.2 $(M+H)^+$
311		462.5 $(M+H)^+$
312		474.2 $(M+H)^+$

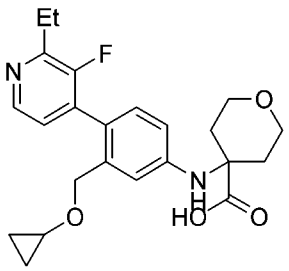
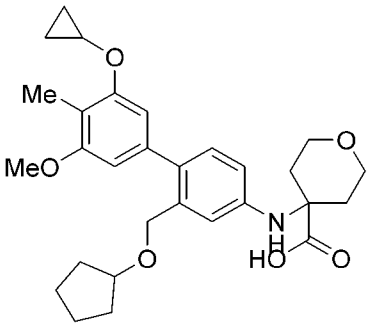
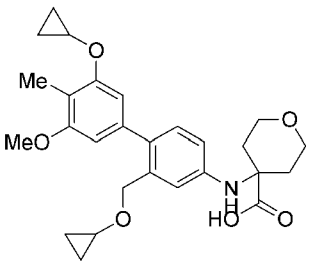
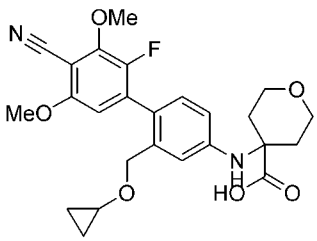
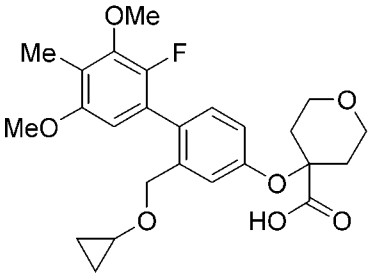
Compound	Structure	LC-MS: m/z
313		440.1 $(M+H)^+$
314		479.1 $(M+H)^+$
315		470.2 $(M+H)^+$
316		442.1 $(M+H)^+$
317		446.0 $(M+H)^+$

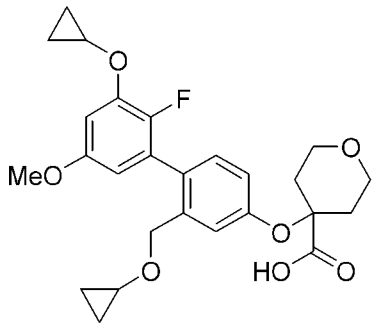
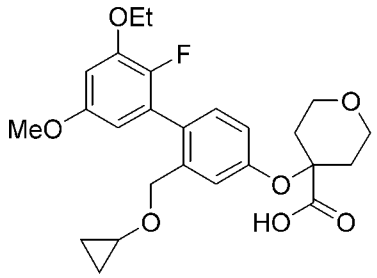
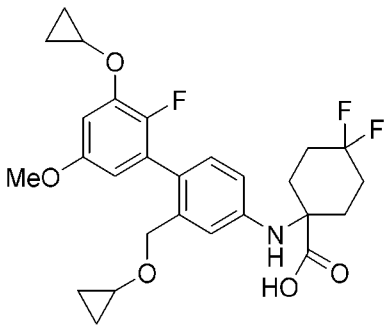
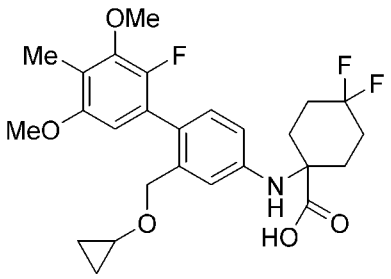
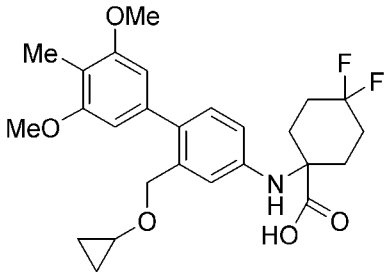
Compound	Structure	LC-MS: m/z
318		456.1 $(M+H)^+$
319		458.6 $(M+H)^+$
320		506.2 $(M+H)^+$
322		474.0 $(M+H)^+$
323		463.5 $(M+H)^+$

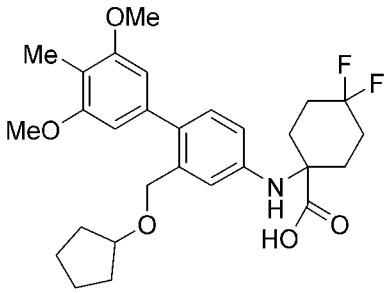
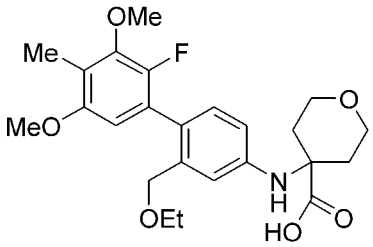
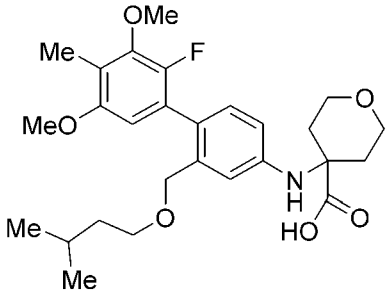
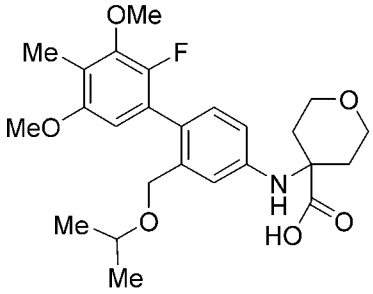
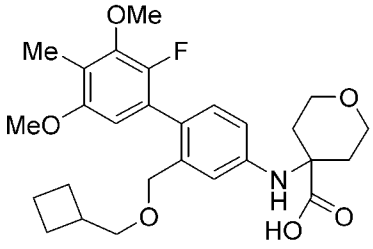
Compound	Structure	LC-MS: m/z
324		443.5 $(M+H)^+$
325		430.2 $(M+H)^+$
326		428.5 $(M+H)^+$
327		414.5 $(M+H)^+$
328		400.5 $(M+H)^+$

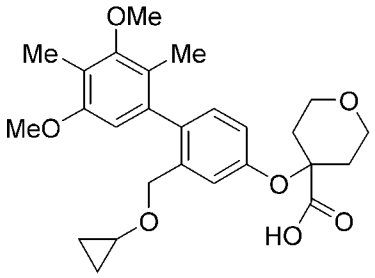
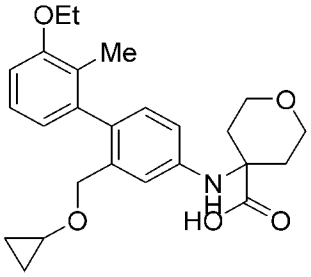
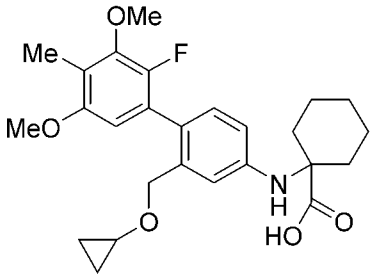
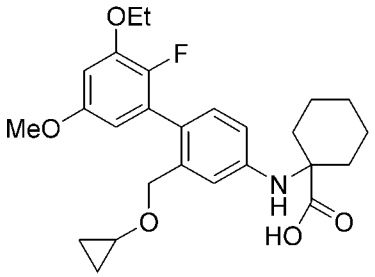
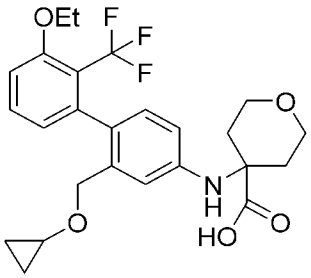
Compound	Structure	LC-MS: m/z
329		456.6 $(M+H)^+$
330		484.6 $(M+H)^+$
331		482.1 $(M+H)^+$
332		454.0 $(M+H)^+$
333		432.1 $(M+H)^+$

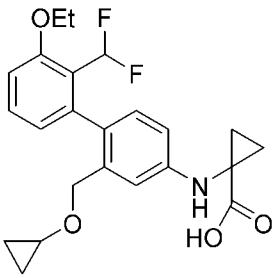
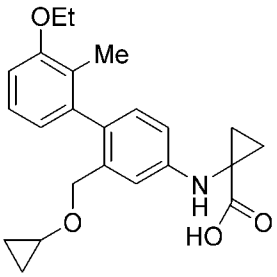
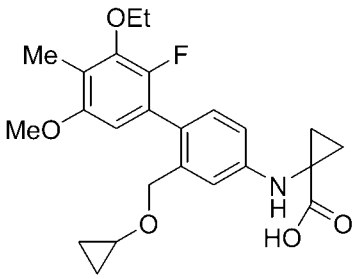
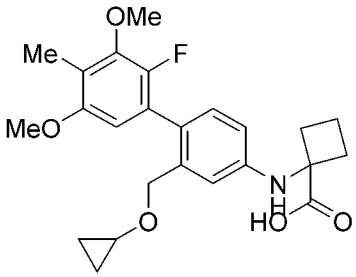
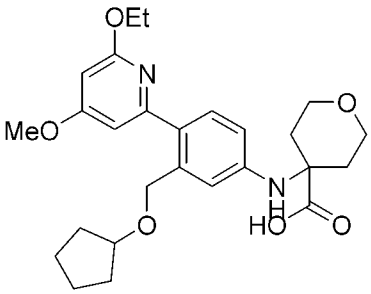
Compound	Structure	LC-MS: m/z
334		462.6 $(M+H)^+$
335		476.6 $(M+H)^+$
336		476.6 $(M+H)^+$
337		438.1 $(M+Na)^+$
338		463.3 $(M+H)^+$

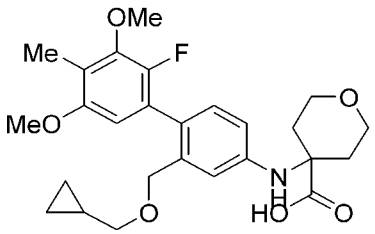
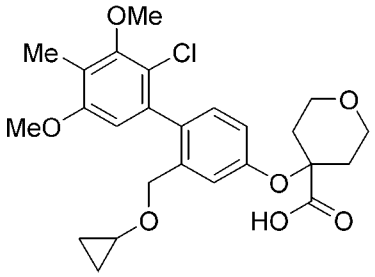
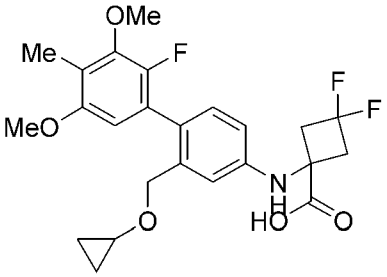
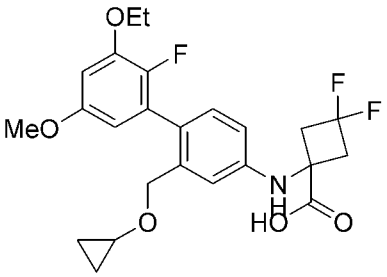
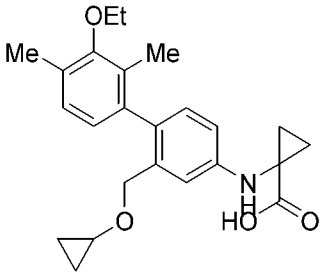
Compound	Structure	LC-MS: m/z
339		415.2 $(M+H)^+$
340		496.6 $(M+H)^+$
341		468.2 $(M+H)^+$
342		471.2 $(M+H)^+$
343		483.1 $(M+Na)^+$

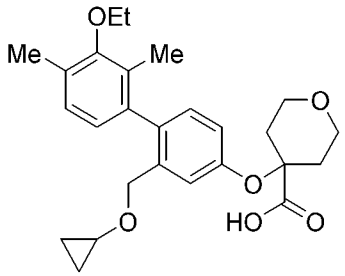
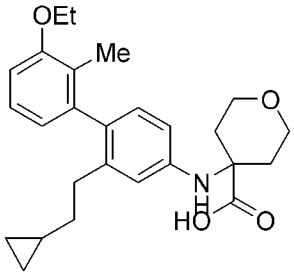
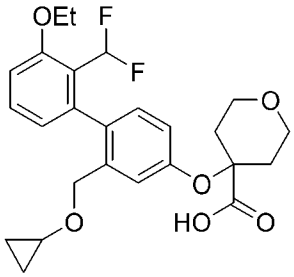
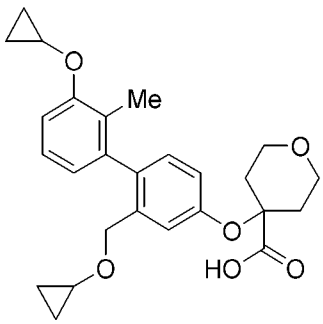
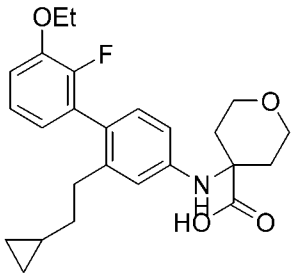
Compound	Structure	LC-MS: m/z
344		495.0 $(M+Na)^+$
345		483.1 $(M+Na)^+$
346		506.6 $(M+H)^+$
347		494.3 $(M+H)^+$
348		476.3 $(M+H)^+$

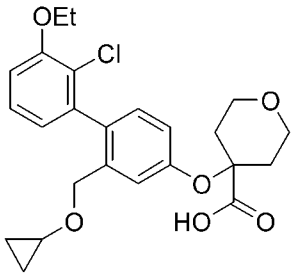
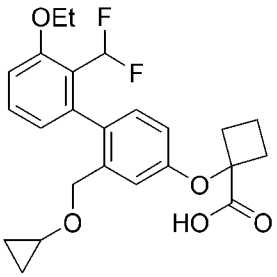
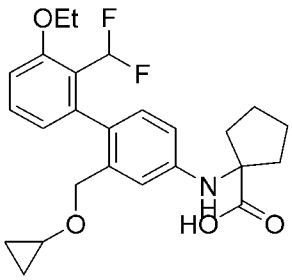
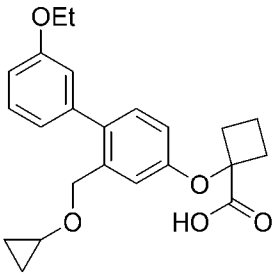
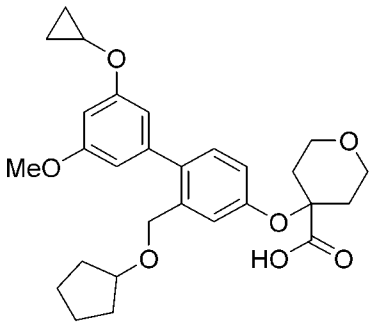
Compound	Structure	LC-MS: m/z
349		504.6 $(M+H)^+$
350		448.5 $(M+H)^+$
351		490.3 $(M+H)^+$
352		462.1 $(M+H)^+$
353		488.3 $(M+H)^+$

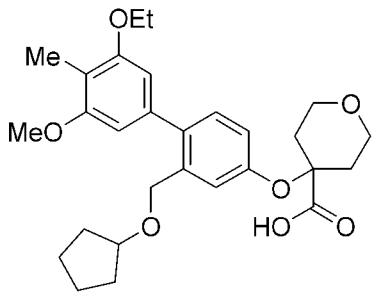
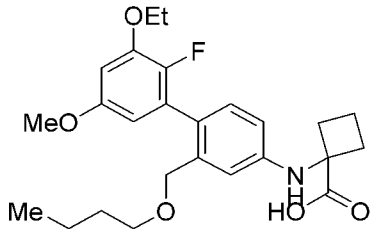
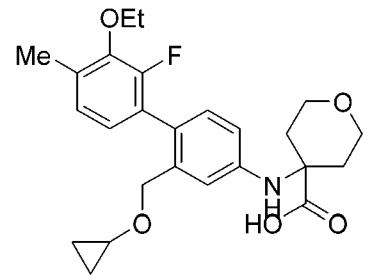
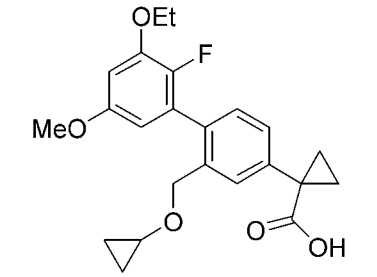
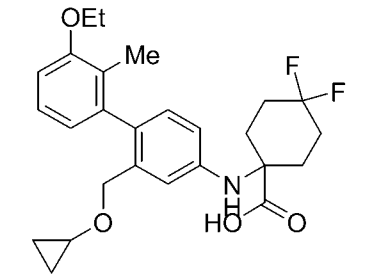
Compound	Structure	LC-MS: m/z
354		479.2 $(M+Na)^+$
355		426.5 $(M+H)^+$
356		458.1 $(M+H)^+$
357		458.1 $(M+H)^+$
358		480.1 $(M+H)^+$

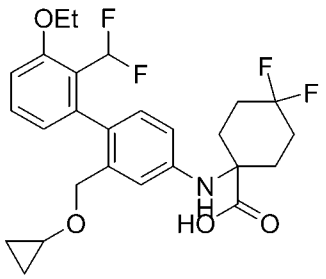
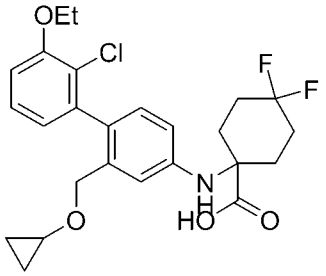
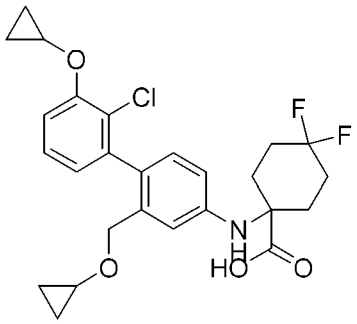
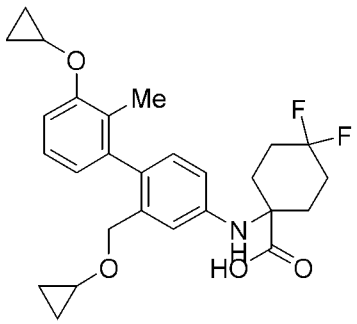
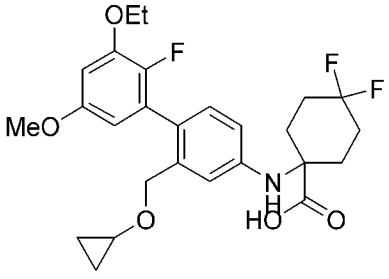
Compound	Structure	LC-MS: m/z
359		440.1 $(M+Na)^+$
360		404.1 $(M+Na)^+$
361		430.1 $(M+H)^+$
362		430.1 $(M+H)^+$
363		471.5 $(M+H)^+$

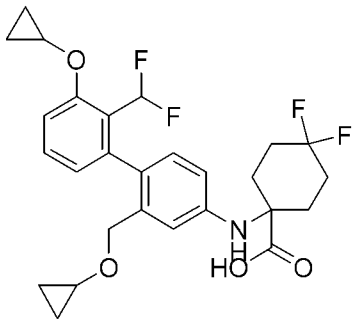
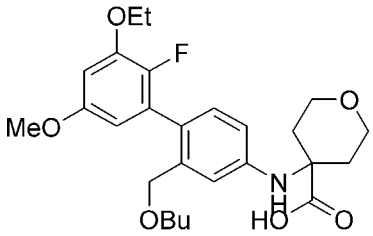
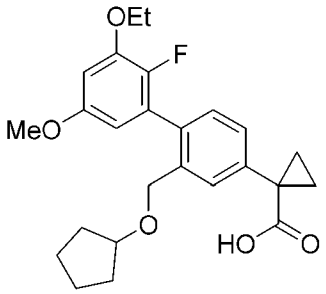
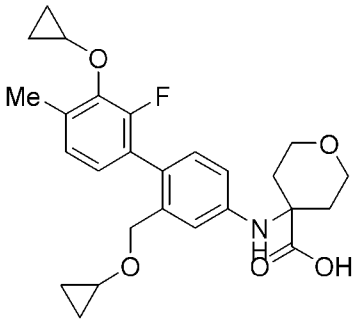
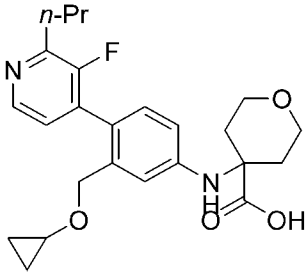
Compound	Structure	LC-MS: m/z
364		474.6 $(M+H)^+$
365		499.0 $(M+Na)^+$
366		466.1 $(M+H)^+$
367		466.1 $(M+H)^+$
368		396.1 $(M+H)^+$

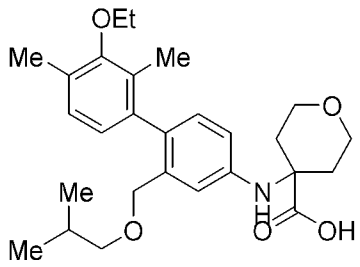
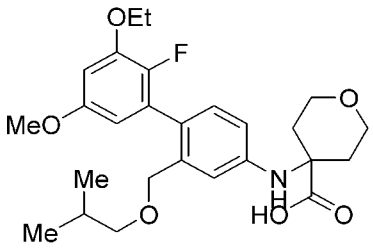
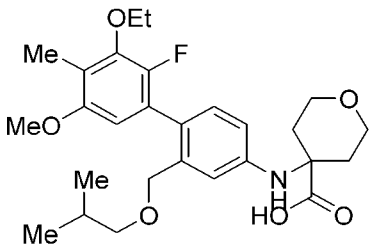
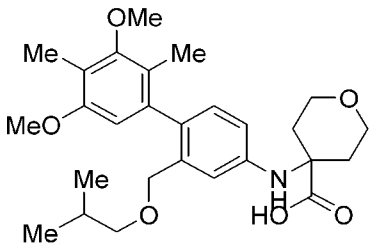
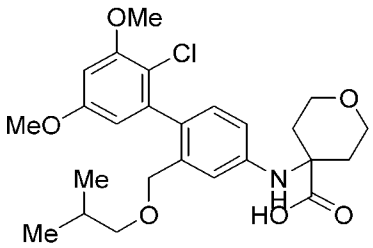
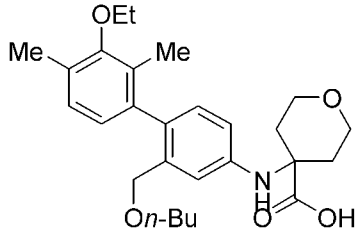
Compound	Structure	LC-MS: m/z
369		463.1 $(M+Na)^+$
370		424.1 $(M+H)^+$
371		485.0 $(M+Na)^+$
372		461.2 $(M+Na)^+$
373		428.0 $(M+H)^+$

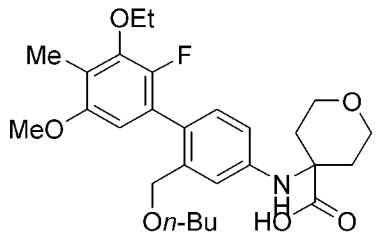
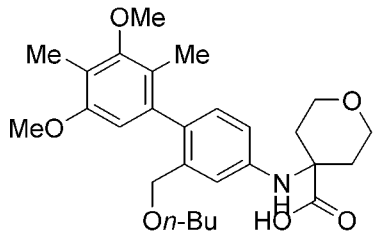
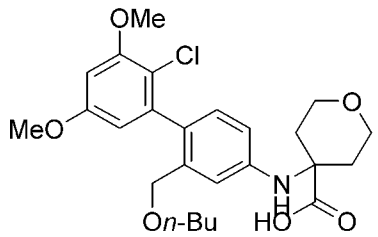
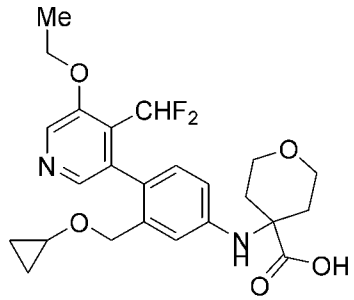
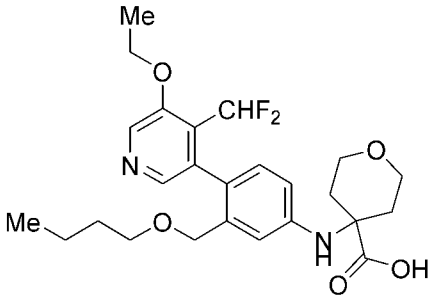
Compound	Structure	LC-MS: m/z
374		469.1 $(M+Na)^+$
375		455.1 $(M+Na)^+$
376		446.1 $(M+H)^+$
377		405.1 $(M+Na)^+$
378		505.3 $(M+Na)^+$

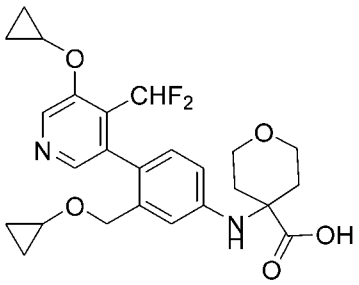
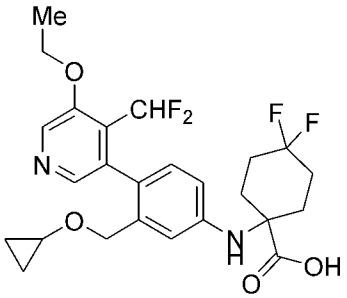
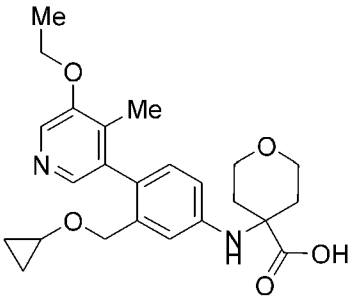
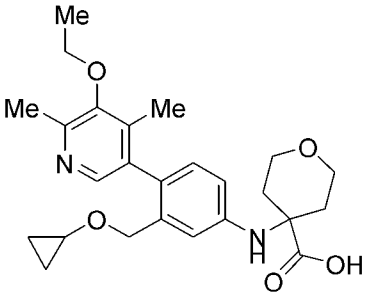
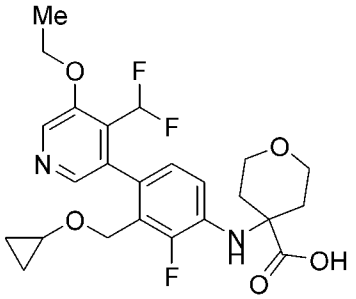
Compound	Structure	LC-MS: m/z
379		502.4 $(M+NH_4)^+$
380		446.0 $(M+H)^+$
381		444.1 $(M+H)^+$
382		418.5 $(M+NH_4)^+$
383		460.1 $(M+H)^+$

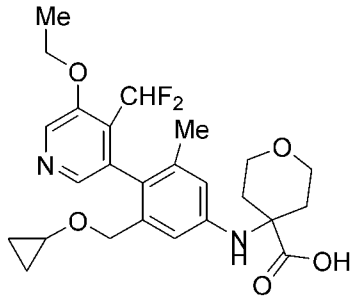
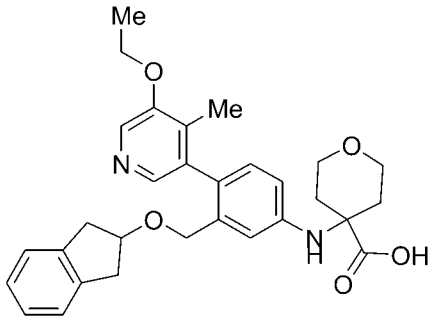
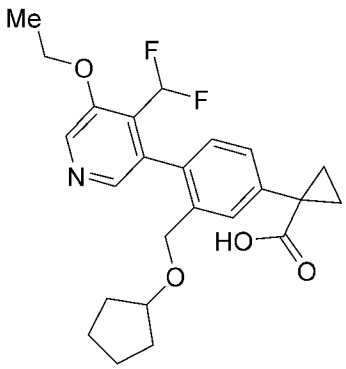
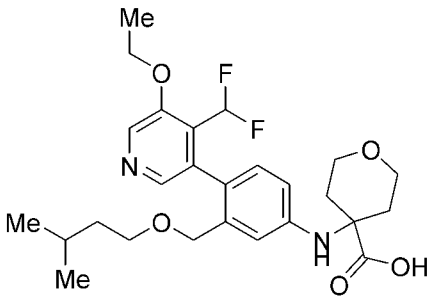
Compound	Structure	LC-MS: m/z
384		496.1 $(M+H)^+$
385		480.1 $(M+H)^+$
386		492.5 $(M+H)^+$
387		472.6 $(M+H)^+$
388		494.2 $(M+H)^+$

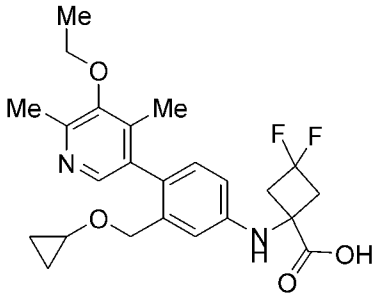
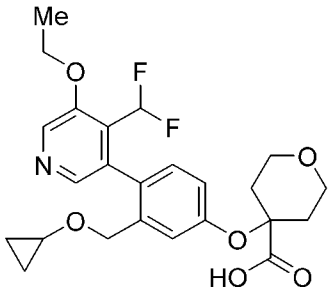
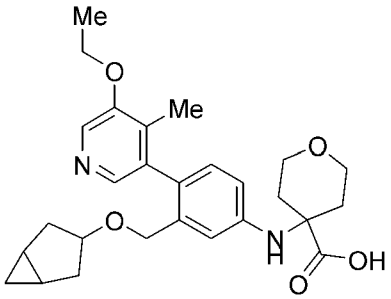
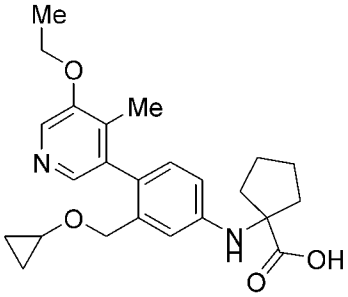
Compound	Structure	LC-MS: m/z
389		508.1 $(M+H)^+$
390		476.2 $(M+H)^+$
391		446.6 $(M+NH_4)^+$
392		456.1 $(M+H)^+$
393		429.5 $(M+H)^+$

Compound	Structure	LC-MS: m/z
394		456.6 $(M+H)^+$
395		476.6 $(M+H)^+$
396		490.6 $(M+H)^+$
397		472.6 $(M+H)^+$
398		478.5 $(M+H)^+$
399		456.1 $(M+H)^+$

Compound	Structure	LC-MS: m/z
400		490.6 $(M+H)^+$
401		472.2 $(M+H)^+$
402		478.1 $(M+H)^+$
403		463.5 $(M+H)^+$
404		479.0 $(M+H)^+$

Compound	Structure	LC-MS: m/z
405		475.1 $(M+H)^+$
406		497.2 $(M+H)^+$
407		427.2 $(M+H)^+$
408		441.1 $(M+H)^+$
409		481.0 $(M+H)^+$

Compound	Structure	LC-MS: m/z
410		477.2 $(M+H)^+$
411		503.6 $(M+H)^+$
412		432.5 $(M+H)^+$
413		493.6 $(M+H)^+$

Compound	Structure	LC-MS: m/z
414		447.1 $(M+H)^+$
415		464.1 $(M+H)^+$
416		467.5 $(M+H)^+$
417		411.5 $(M+H)^+$

Biological Assays

In Vitro LPA1 functional antagonist Assay

[0571] CHO-K1 cells overexpressing human LPA1 were seeded in a total volume of 20 μL into black-walled, clear-bottom, Poly-D-lysine coated 384-well microplates and incubated at 37°C for the appropriate time prior to testing. Assays were performed in 1 x Dye Loading Buffer consisting of 1x Dye, 1x Additive A and 2.5 mM Probenecid in HBSS / 20 mM Hepes. Probenicid was prepared fresh. Cells

were loaded with dye prior to testing. Media was aspirated from cells and replaced with 20 µL Dye Loading Buffer. Cells were incubated for 30-60 minutes at 37°C. After dye loading, cells were removed from the incubator and 10 µL 3X test compound was added. Cells were incubated for 30 minutes at room temperature in the dark to equilibrate plate temperature followed by Oleoyl LPA challenge at EC_{80}. Compound antagonist activity was measured on a FLIPR Tetra (MSD). Calcium mobilization was monitored for 2 minutes and 10 µL Oleoyl LPA in HBSS / 20 mM Hepes was added to the cells 5 seconds into the assay. For LPA EC_{80} determination, after dye loading, cells were removed from the incubator and 10 µL HBSS / 20 mM Hepes was added. 3X vehicle was included in the buffer. Cells were incubated for 30 minutes at room temperature in the dark to equilibrate plate temperature. Intermediate dilution of LPA stocks was performed to generate 4X LPA samples in assay buffer. LPA agonist activity was measured on a FLIPR Tetra (MSD). Calcium mobilization was monitored for 2 minutes and 10 µL 4X LPA sample in HBSS / 20 mM Hepes was added to the cells 5 seconds into the assay. Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). Percentage inhibition is calculated using the following formula:

% Inhibition =100% x (1 - (mean RFU of test sample - mean RFU of vehicle control) / (mean RFU of LPA control - mean RFU of vehicle control)).

[0572] **Table B1** and **Table B2** show the biological activity of compounds in in vitro LPA1 functional antagonist assay. Activity of the tested compounds provided in **Table B1** is as follows: +++ = IC_{50} < 1 µM; ++ = IC_{50} 1 µM – 10 µM; + = IC_{50} > 10 µM. Activity of the tested compounds provided in **Table B2** is in µM.

Table B1

Compound	Activity
101	+++
102	++

Compound	Activity
103	++
104	+++

Compound	Activity
105	+++
109	+++

Table B2

Compound	IC_{50} (µM)
101	0.0272
102	2.49
103	1.54
104	0.162

Compound	IC_{50} (µM)
105	0.0136
109	0.00268
185	0.00954
256	0.0103

Compound	IC_{50} (µM)
280	0.0186
282	0.00888
283	0.0109
284	0.00397

Compound	IC_{50} (μM)
285	0.00662
294	0.00715

Compound	IC_{50} (μM)
295	0.00794
298	0.00264

Compound	IC_{50} (μM)
355	0.00753

In vitro LPA1 Calcium flux antagonist assay – Bioduro protocol

[0573] CHO-K1 cells overexpressing human LPA1 and G15a were seeded at a total volume of 20 μL (15000 cells/well) into Matrigel pre-coated 384-well plates (corning -3764) and incubated at 37°C. After overnight incubation, the cells were serum starved for 4h. Assays were performed in dye loading buffer containing 1x Fluo-8 AM (AAT Bioquest, 21080) and 2.5 mM probenecid (Thermo Fisher, 36400) in HBSS / 20 mM Hepes. After cell starvation, the medium was replaced with 20 μL of dye loading buffer and incubated at 37°C for 30 min. Then 5 μL of 5X compound titrated in dye loading buffer was added to the cells and incubated for 30 min followed by LPA challenge at EC80. Calcium mobilization was measured on a FLIPR Tetra (MSD). For LPA EC80 determination, starved cells were incubated with 20 μL of dye loading buffer for 1h, then 5 μL of 5X LPA titrated in dye loading buffer was added to the cells. Calcium signals induced by LPA was monitors on a FLIPR.

[0574] Percentage inhibition is calculated using the following formula:

% Inhibition =100% x (1 - (mean RFU of test sample - mean RFU of DMSO) / (mean RFU of LPA control - mean RFU of DMSO)).

[0575] **Table B3** and **Table B4** show the biological activity of compounds in *in vitro* LPA1 Calcium flux antagonist assay – Bioduro protocol. Activity of the tested compounds provided in **Table B3** below as follows: +++ = IC_{50} < 100 nM; ++ = IC_{50} 100 nM - 1 μM; + = IC_{50} > 1 μM. Activity of the tested compounds provided in **Table B4** is in nM.

Table B3

Compound	Activity
101	++
104	++
105	++
106	+
107	+
108	+
109	+++

Compound	Activity
110	++
111	+++
112	++
113	+
114	++
115	+
116	+

Compound	Activity
117	+++
118	+++
119	+++
120	+++
121	+++
122	++
123	+++

Compound	Activity
124	+++
125	++
126	+++
127	+++
128	+++
129	+++
130	++
131	++
132	+++
133	+++
134	+++
135	+++
136	+
137	+++
138	++
139	++
140	+++
141	+++
142	+
143	+++
144	+++
145	++
146	+++
147	+++
148	+++
149	+++
151	+
152	++
153	+
154	++
155	++
156	++

Compound	Activity
157	++
158	+++
159	+
160	++
161	++
163	++
164	+
165	+++
166	+++
168	+++
169	+
170	+
171	+
172	+++
173	++
174	+++
175	++
176	++
178	+
179	+++
180	+++
181	+++
182	+++
184	+++
185	+++
186	+++
188	+
189	+++
190	+++
191	+++
192	+++
193	+++

Compound	Activity
194	+++
195	+
196	+++
197	+++
198	++
199	+
200	++
201	+++
202	+
203	+++
204	++
205	+
206	++
207	+++
208	+++
209	+++
210	+
211	+
212	+++
213	+++
214	+++
215	+++
216	+++
217	++
218	+
219	+++
220	++
222	++
223	+++
224	++
225	++
226	+++

Compound	Activity
227	+++
228	+++
229	+++
230	++
232	++
233	++
234	+
235	++
236	+
237	+++
238	++
239	++
240	+++
241	++
242	++
243	++
244	+++
245	+++
246	+++
247	+
248	+++
249	+++
250	+++
251	+++
252	+++
253	+++
254	++
255	+
256	+++
257	+++
259	+++
260	++

Compound	Activity
261	+++
262	+++
263	+++
264	+++
265	+++
266	++
267	+++
268	++
269	++
270	+++
271	+++
272	+++
273	+++
274	+++
275	++
276	+++
277	+++
278	+++
279	+++
280	+++
281	++
282	+++
283	+++
284	+++
285	+++
286	+++
287	+++
288	+++
289	+++
290	+++
291	+++
292	++

Compound	Activity
293	+++
294	+++
295	+++
296	+++
297	++
298	+++
299	+++
300	+++
301	+++
302	++
303	+++
304	+
305	+
306	++
307	+++
308	+++
309	+++
310	+++
311	++
312	+++
313	+++
314	+++
315	+++
316	+
317	+++
318	+++
319	+++
320	+++
322	+++
323	++
324	+
325	+++

Compound	Activity
326	++
327	++
328	+
329	+++
330	+++
331	+++
332	+++
333	+++
334	+++
335	+++
336	+++
337	++
338	+++
339	+++
340	+++
341	++
342	+++
343	+
344	++
345	++
346	+++
347	+++
348	+++
349	+++
350	+
351	+++
352	+++
353	+++
354	+++
355	+++
356	+++

Compound	Activity
357	+++
358	+++
359	+++
360	+++
361	+++
362	++
363	+
364	+++
365	+++
366	+++
367	+++
368	+++
369	+++
370	+++
371	+++
372	+++
373	+++
374	+++
375	+++
376	+++
377	+
378	++
379	+++
380	+++
381	+++
382	+
383	+++
384	+++
385	+++
386	+++
387	+++

Compound	Activity
388	+++
389	+++
390	+++
391	++
392	+++
393	+
394	+++
395	+++
396	+++
397	+++
398	++
399	+++
400	+++
401	+++
402	+++
403	+++
404	+++
405	+++
406	+++
407	+++
408	++
409	++
410	++
411	+++
412	++
413	+++
414	++
415	+++
416	+++
417	+++

Table B4

Compound	IC_{50} (nM)	Compound	IC_{50} (nM)	Compound	IC_{50} (nM)
101	340	**130**	191	**158**	46.3
104	628	**131**	190	**159**	>10000
105	245	**132**	20.1	**160**	666
106	3480	**133**	82.9	**161**	976
107	2580	**134**	90.6	**163**	382
108	1880	**135**	27.8	**164**	>10000
109	94.1	**136**	885	**165**	10.9
110	152	**137**	45.2	**166**	9.31
111	19.8	**138**	174	**168**	27.6
112	188	**139**	353	**169**	>10000
113	7130	**140**	28.8	**170**	1500
114	248	**141**	24.5	**171**	>10000
115	6820	**142**	>10000	**172**	82.1
116	2160	**143**	53.8	**173**	314
117	60.5	**144**	59.5	**174**	29.3
118	96.4	**145**	486	**175**	175
119	35.6	**146**	77.2	**176**	883
120	57	**147**	20.9	**178**	1320
121	13.5	**148**	10.5	**179**	24.9
122	112	**149**	88	**180**	39.7
123	14.8	**151**	1580	**181**	55.2
124	91.6	**152**	390	**182**	9.7
125	116	**153**	>10000	**184**	33.2
126	32.1	**154**	224	**185**	12.6
127	16.3	**155**	252	**186**	64.3
128	31.4	**156**	162	**188**	2730
129	17.2	**157**	112	**189**	52.5

Compound	IC_{50} (nM)
190	27
191	34.3
192	15.1
193	31.9
194	79.8
195	760
196	30.1
197	12.5
198	232
199	3210
200	772
201	73.2
202	>10000
203	26
204	163
205	1260
206	476
207	30.4
208	56.4
209	15.5
210	>10000
211	>10000
212	11.2
213	58.7
214	58.9
215	10.8
216	18.6
217	584

Compound	IC_{50} (nM)
218	>10000
219	58
220	81.6
222	167
223	4.76
224	158
225	320
226	22.2
227	25
228	2.63
229	5.28
230	139
232	756
233	914
234	5190
235	198
236	4710
237	63.6
238	268
239	970
240	23.4
241	87
242	266
243	82.9
244	2.73
245	23.2
246	24.3
247	1610

Compound	IC_{50} (nM)
248	50.2
249	1.13
250	31.7
251	40.2
252	14.9
253	54.3
254	370
255	2390
256	16.5
257	8.41
259	81.3
260	174
261	51.9
262	30.8
263	60.4
264	5.42
265	12
266	142
267	68
268	648
269	259
270	79.8
271	21.4
272	6.96
273	17.1
274	28
275	229
276	25.4

Compound	IC_{50} (nM)
277	72.7
278	36.6
279	4.19
280	8.12
281	110
282	25.7
283	11.5
284	11.9
285	13.9
286	9.87
287	2.46
288	11.9
289	51
290	15.8
291	173
292	117
293	5.72
294	5.85
295	3.31
296	2.4
297	137
298	0.763
299	38.4
300	35.3
301	12.5
302	85.2
303	12.3
304	5.64

Compound	IC_{50} (nM)
305	711
306	165
307	58.4
308	23.6
309	37.7
310	6.93
311	148
312	5.44
313	5.93
314	37
315	24
316	1080
317	14
318	9.47
319	76.7
320	12.1
322	5.9
323	833
324	>10000
325	59.6
326	124
327	412
328	>10000
329	61.9
330	9.53
331	9.37
332	139
333	10.3

Compound	IC_{50} (nM)
334	45.2
335	5.56
336	18.8
337	315
338	17.2
339	85.3
340	26.1
341	214
342	19.7
343	1130
344	106
345	144
346	7.24
347	23.5
348	69.5
349	14.2
350	4320
351	4.63
352	75
353	8.39
354	35.5
355	3.02
356	47.4
357	30.3
358	5.37
359	49.8
360	75.5
361	75.6

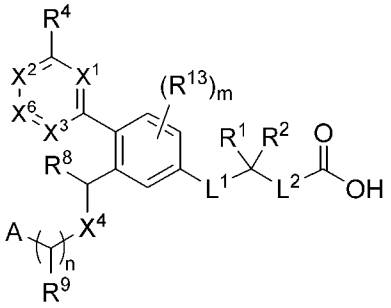
Compound	IC_{50} (nM)
362	356
363	4850
364	82.9
365	18.7
366	55
367	33.2
368	40.7
369	44.8
370	1.95
371	22.3
372	57.4
373	1.2
374	14.6
375	24.3
376	1.03
377	>10000
378	834
379	67.3
380	17.4

Compound	IC_{50} (nM)
381	17.5
382	>10000
383	0.847
384	0.803
385	0.633
386	3.84
387	4.39
388	6.2
389	0.772
390	0.658
391	471
392	9.44
393	>10000
394	97.6
395	7.94
396	27.5
397	73
398	104
399	6.41

Compound	IC_{50} (nM)
400	5.37
401	5.71
402	7.59
403	23.1
404	13
405	65
406	20
407	96.5
408	152
409	229
410	179
411	5.2
412	538
413	5.79
414	112
415	66.2
416	8.79
417	35.8

CLAIMS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of A is independently optionally substituted with one to five Z^1;

L^1 is a bond, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR^{10}-, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^1 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

L^2 is a bond, C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene; wherein the C_{1-3} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, or C_{1-3} heteroalkylene of L^2 is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, halo, hydroxy, and cyano;

X^1 is N or CR^3;

X^2 is N or CR^5;

X^3 is N or CR^7;

X^4 is O or CHR^{11}; provided that when A is C_{1-6} alkyl, then X^4 is O;

X^6 is N or CR^6;

n is 0, 1, or 2;

m is 0, 1, 2, or 3;

R^1 and R^2 are each independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl of R^1 and R^2 are independently optionally substituted with one to five Z^1;

or R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-10} cycloalkyl or heterocyclyl; wherein the C_{3-10} cycloalkyl or heterocyclyl is optionally substituted by one to five Z^1;

R^3 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^3 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^4 is halo, cyano, nitro, -OR^{14}, -N(R^{14})$_2$, -SR^{14}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^4 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, C_{1-5} alkoxy, and cyano;

or R^3 and R^4 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^5 is hydrogen, halo, cyano, nitro, -OR^{15}, -N(R^{15})$_2$, -SR^{15}, -C(O)R^{15}, -C(O)OR^{15}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, 3-5 membered heterocyclyl or 5 membered heteroaryl of R^5 is independently optionally substituted with one to five Z^1;

R^6 is hydrogen, halo, cyano, nitro, -OR^{16}, -N(R^{16})$_2$, -SR^{16}, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^6 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^7 is hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the -NH-C_{1-5} alkyl, -N(C_{1-5} alkyl)$_2$, -S-C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^7 is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

or R^6 and R^7 are taken together with the atoms to which they are attached to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl; wherein the cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^8 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^9 is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

R^{10} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{10} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{11} is hydrogen, C_{1-9} alkyl, oxo, halo, hydroxy, or cyano;

each R^{13} is independently hydrogen, halo, cyano, nitro, -OH, -SH, $-NH_2$, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-6} cycloalkyl, or 3 to 6-membered heterocyclyl of R^{13} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{14} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{14} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{15} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{15} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

R^{16} is hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl; wherein the C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-5} cycloalkyl, or 3-5 membered heterocyclyl of R^{16} is independently optionally substituted with one to five substituents independently selected from halo, hydroxy, and cyano;

each Z^1 is independently halo, cyano, nitro, oxo, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-H, -L-C_{1-9} alkyl, -L-C_{2-9} alkenyl, -L-C_{2-9} alkynyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl,

C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^1 is independently optionally substituted with one to five Z^{1a};

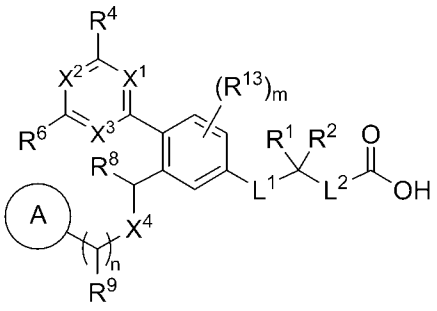
each L is independently -O-, -S-, -NR^{20}-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NR^{20}-, -NR^{20}C(O)-, -OC(O)NR^{20}-, -NR^{20}C(O)O-, -NR^{20}C(O)NR^{21}-, -S(O)-, -$S(O)_2$-, -S(O)NR^{20}-, -$S(O)_2NR^{20}$-, -NR^{20}S(O)-, -$NR^{20}S(O)_2$-, -NR^{20}S(O)NR^{21}-, or -$NR^{20}S(O)_2NR^{21}$-;

each R^{20} and R^{21} is independently hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{20} and R^{21} is independently optionally substituted with one to five Z^{1a}; or an R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to five Z^{1a}; and

each Z^{1a} is independently halo, hydroxy, cyano, nitro, oxo, -SH, -NH_2, -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each -NH-C_{1-9} alkyl, -N(C_{1-9} alkyl)$_2$, -S-C_{1-9} alkyl, C_{1-9} alkoxy, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1a} is independently optionally substituted with one to five substituents independently selected from C_{1-9} alkyl, oxo, halo, hydroxy, and cyano.

2. The compound of claim 1, wherein A is C_{1-6} alkyl.

3. The compound of claim 1, represented by Formula IIA:



IIA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein ring A is C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; and each C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of ring A is independently optionally substituted with one to five Z^1.

4. The compound of claim 1 or 3, wherein A or ring A is C_{3-10} cycloalkyl optionally substituted with one to five Z^1.

5. The compound of claim 1 or 3, wherein A or ring A is heterocyclyl optionally substituted with one to five Z^1.

6. The compound of claim 1 or 3, wherein A or ring A is aryl optionally substituted with one to five Z^1.

7. The compound of claim 1 or 3, wherein A or ring A is heteroaryl optionally substituted with one to five Z^1.

8. The compound of claim 1 or 3, wherein A or ring A is C_{3-10} cycloalkyl or heteroaryl.

9. The compound of any preceding claim, wherein L^1 is a bond, -O-, -NR^{10}-, C_{1-3} alkylene, or C_{1-3} heteroalkylene.

10. The compound of any preceding claim, wherein L^2 is a bond.

11. The compound of any preceding claim, wherein X^1 is CR^3.

12. The compound of any preceding claim, wherein R^3 is hydrogen, halo, or C_{1-5} alkyl, wherein the C_{1-5} alkyl is optionally substituted with one to five halo.

13. The compound of any one of claims 1-10, wherein X^1 is N.

14. The compound of any preceding claim, wherein R^4 is -OR^{14} or C_{1-5} alkyl, wherein the C_{1-5} alkyl is optionally substituted with hydroxy or C_{1-5} alkoxy.

15. The compound of any preceding claim, wherein R^4 is hydroxy, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, cyclopropoxy, cyclobutoxy, methyl, ethyl, *n*-propyl, *iso*-propyl, 2-hydroxyethyl, or methoxymethyl.

16. The compound of any preceding claim, wherein X^2 is CR^5.

17. The compound of any preceding claim, wherein R^5 is hydrogen, halo, cyano, -C(O)-C_{1-5} alkyl, or C_{1-5} alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, and C_{1-5} alkoxy.

18. The compound of any preceding claim, wherein R^6 is hydrogen, cyano, hydroxy, C_{1-5} alkoxy, or C_{1-5} alkyl.

19. The compound of any one of claims 1-15, wherein X^2 is N.

20. The compound of any preceding claim, wherein X^3 is CR^7.

21. The compound of any preceding claim, wherein R^7 is hydrogen, halo, C_{1-5} alkyl, or C_{1-5} haloalkyl.

22. The compound of any one of claims 1-19, wherein X^3 is N.

23. The compound of any preceding claim, wherein X^4 is O.

24. The compound of any preceding claim, wherein R^8 is hydrogen.

25. The compound of any preceding claim, wherein n is 0.

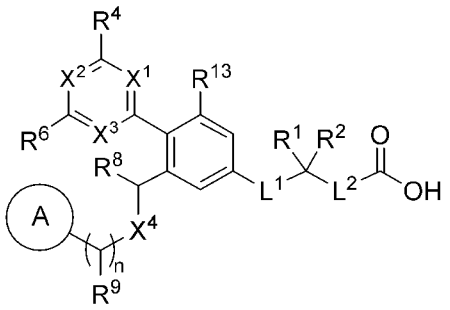
26. The compound of any preceding claim, wherein R^1 and R^2 are each independently C_{1-9} alkyl.

27. The compound of any one of claims 1-25, wherein R^1 and R^2 are taken together with the atom to which they are attached to form a C_{3-10} cycloalkyl optionally substituted by one to five Z^1.

28. The compound of any one of claims 1-25, wherein R^1 and R^2 are taken together with the atom to which they are attached to form a heterocyclyl optionally substituted by one to five Z^1.

29. The compound of any preceding claim, wherein R^{13} is hydrogen, halo, or C_{1-9} alkyl.

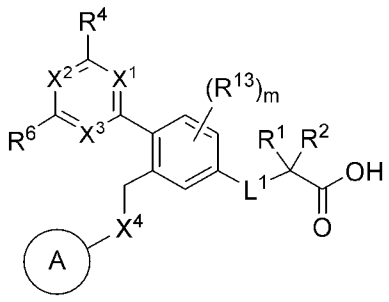
30. The compound of claim 1 or 3, represented by Formula IA:



IA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof.

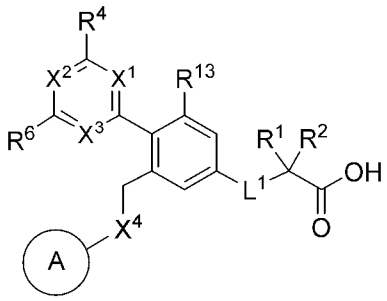
31. The compound of claim 1 or 3, represented by Formula IF:



IF

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof.

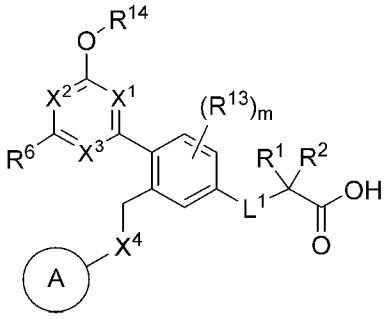
32. The compound of claim 1 or 3, represented by Formula IH:



IH

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof.

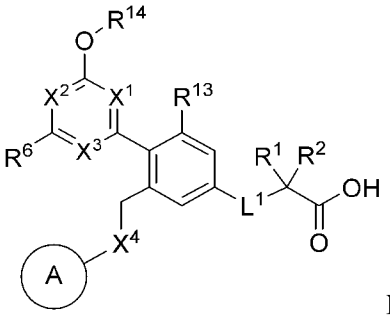
33. The compound of claim 1 or 3, represented by Formula IK:



IK

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof.

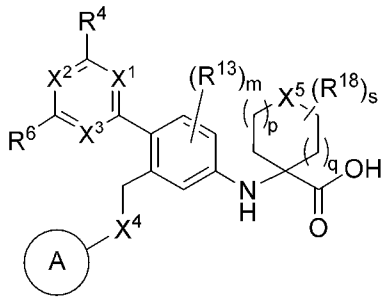
34. The compound of claim 1 or 3, represented by Formula IM:



IM

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof.

35. The compound of claim 1 or 3, represented by Formula IIIA:



IIIA

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

p is 0, 1, or 2;

q is 0, 1, or 2;

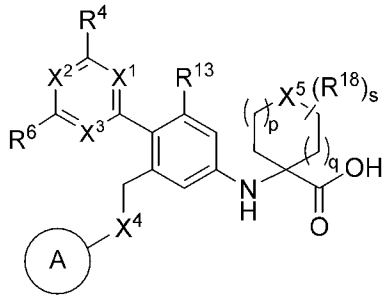
s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

36. The compound of claim 1 or 3, represented by Formula IIIC:



IIIC

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

p is 0, 1, or 2;

q is 0, 1, or 2;

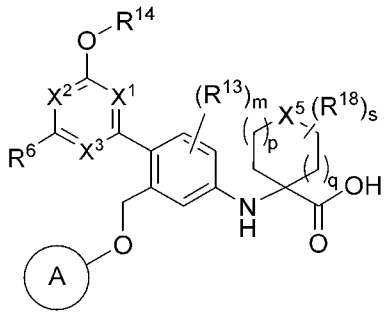
s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

37. The compound of claim 1 or 3, represented by Formula IIID:



IIID

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

p is 0, 1, or 2;

q is 0, 1, or 2;

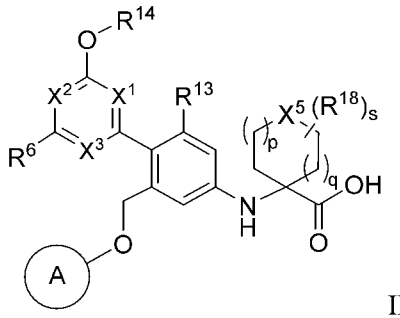
s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

38. The compound of claim 1 or 3, represented by Formula IIIF:



IIIF

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, wherein:

p is 0, 1, or 2;

q is 0, 1, or 2;

s is 0, 1, 2, or 3;

X^5 is absent, O, NR^{17}, or $C(R^{18})_2$;

R^{17} is hydrogen, C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)NR^{20}R^{21}$, or $-S(O)_2NR^{20}R^{21}$; wherein each C_{1-9} alkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{17} is independently optionally substituted with one to five Z^{1a}; and

each R^{18} is independently hydrogen or Z^1.

39. A compound selected from Table 1 or Table 2, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof.

40. A pharmaceutical composition comprising a compound of any preceding claim, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, and a pharmaceutically acceptable carrier.

41. A method for treating a LPA associated disease, disorder, or condition, the method comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1–39, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, isotopically enriched analog, or solvate thereof, or the pharmaceutical composition according to claim 40.

42. The method of claim 41, wherein the LPA-associated disease, disorder, or condition, is a LPA_1-associated disease.

43. The method of claim 41 or 42, wherein the LPA-associated disease, disorder, or condition, is fibrosis, transplant rejection, cancer, osteoporosis, or an inflammatory disorder.

44. The method of claim 43, wherein the fibrosis is pulmonary fibrosis, liver fibrosis, renal fibrosis, cardiac fibrosis, dermal fibrosis, ocular fibrosis, or pancreatic fibrosis.

45. The method of claim 43, wherein the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral mucosa, nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.

46. The method of claim 41 or 42, wherein the LPA-associated disease, disorder, or condition, is idiopathic pulmonary fibrosis (IPF), non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, diabetic kidney disease, systemic sclerosis, COVID-19, chronic obstructive pulmonary disease (COPD), neuroinflammation, or multiple sclerosis.