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(71) Applicant: **LHOTSE BIO, INC.** [US/US]; 611 Gateway Blvd. Suite, 223, South San Francisco, California 94080 (US).

(72) Inventor; and
(71) Applicant *(for SC only)*: **LEI, Hui** [US/CN]; 5 F, JLABS@Shanghai, No. 1 South Bldg., Jin Chuang, 4560 JinKe Rd, Zhangjiang Hi-Tech Park, Shanghai 200003 (CN).

(72) Inventors: **ZHANG, Qiong**; 5 F, JLABS@Shanghai, No. 1 South Bldg., Jin Chuang, 4560 JinKe Rd, Zhangjiang Hi-Tech Park, Shanghai 200003 (CN). **RUVINSKY, Anatoly M.**; 611 Gateway Blvd., Suite 223, South San Francisco, California 94080 (US).

(74) Agent: **WU, FENG & ZHANG**; 3FL, Building 4, Yard 38, LinFengErLu Road, Greenland Central Square, Haidian District, Beijing 100089 (CN).

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

(57) Abstract: It provides LPA antagonists, as well as pharmaceutical compositions comprising the compounds disclosed herein. It also provides 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/CN2022/082072, filed on March 21, 2022, and International Patent Application Number PCT/CN2021/125409, filed October 21, 2021, 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] In one embodiment is provided the compounds of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, is provided the compounds of Table 2, or a pharmaceutically acceptable salt, solvate, stereoisomer, or mixture of stereoisomers thereof.

[0006] Also provided herein are pharmaceutical compositions comprising a compound of Table 1, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutically acceptable salt 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] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] "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., $-CH(CH_3)_2$).

[0030] "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).

[0031] "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.

[0032] 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.

[0033] "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.

[0034] "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.

[0035] "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.

[0036] "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.

[0037] "Alkylthio" refers to the group "alkyl-S-".

[0038] "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.

[0039] "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.

[0040] "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.

[0041] "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.

[0042] "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.

[0043] "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.

[0044] "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.

[0045] "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.

[0046] "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.

[0047] "Halogen" or "halo" refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0048] "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.

[0049] "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, 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, 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]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.

[0050] "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, thiophenyl (i.e., 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.

[0051] "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.

[0052] "Alkylsulfonyl" refers to the group $-S(O)_2R$, where R is alkyl.

[0053] "Alkylsulfinyl" refers to the group -S(O)R, where R is alkyl.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0061] 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.

[0062] The term "pharmaceutical composition" refers to a mixture of a compound disclosed herein, or a pharmaceutically acceptable salt 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

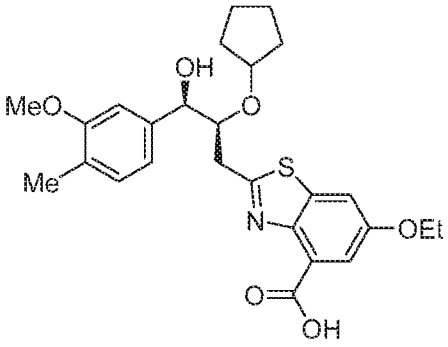
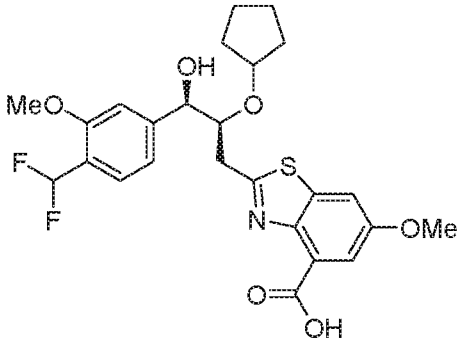
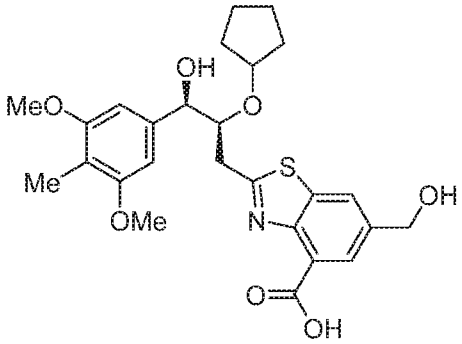
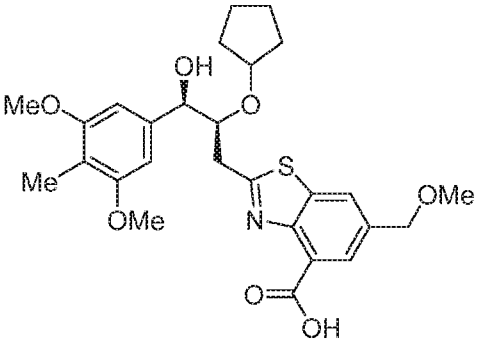
[0068] The term "combination therapy" as used herein refers to a dosing regimen of two different therapeutically active agents (i.e., the components or combination partners of the combination), wherein the therapeutically active agents are administered together or separately in a manner prescribed by a medical care taker or according to a regulatory agency as defined herein.

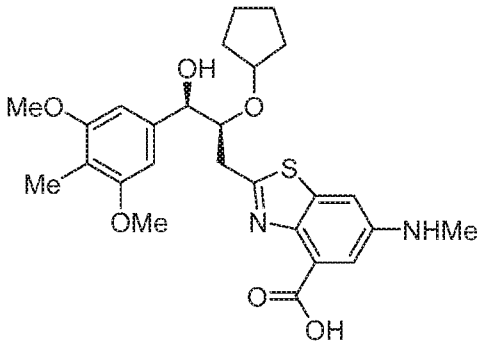
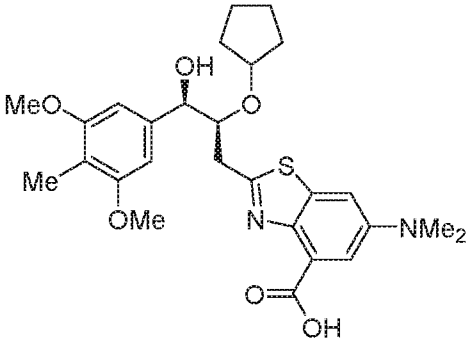
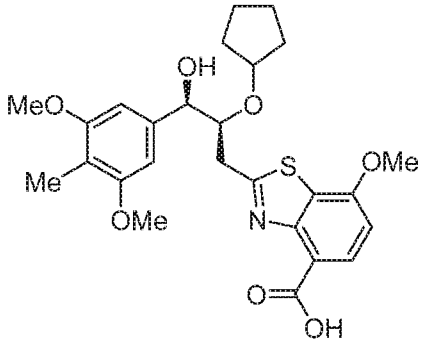
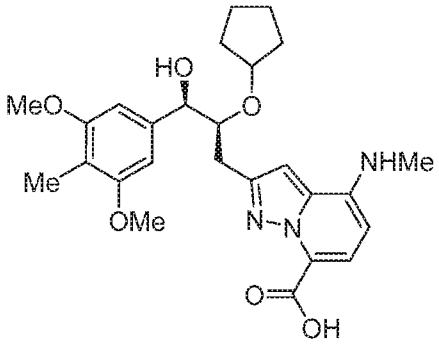
[0069] The term "modulate," "modulating," or "modulation," as used herein, refers to a regulation or an adjustment (e.g., increase or decrease) and can include, for example agonism, partial agonism or antagonism.

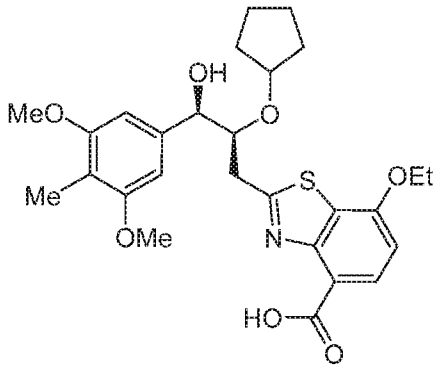
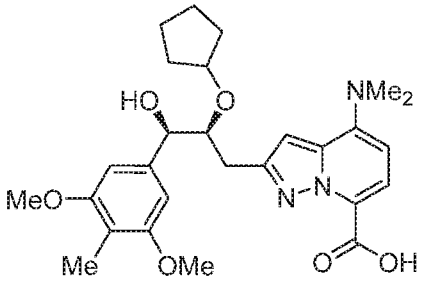
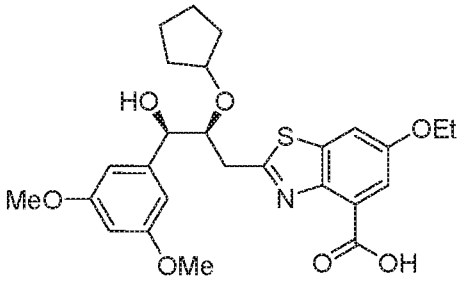
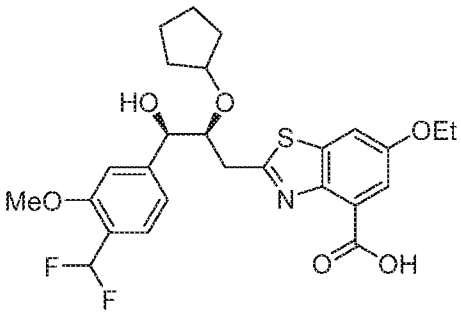
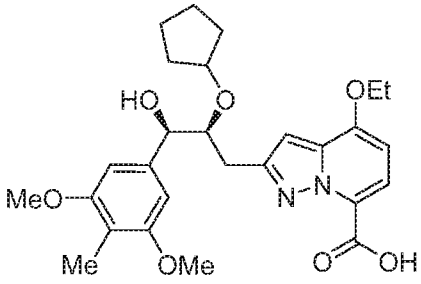
Compounds

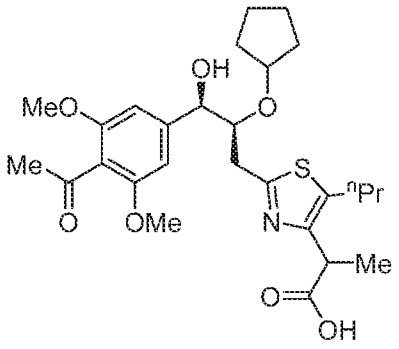
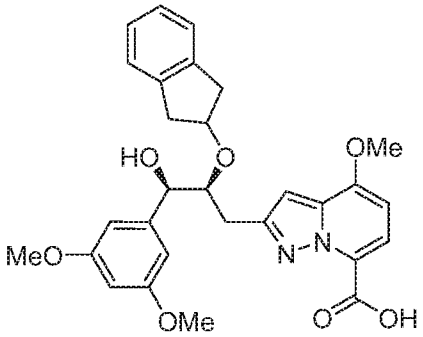
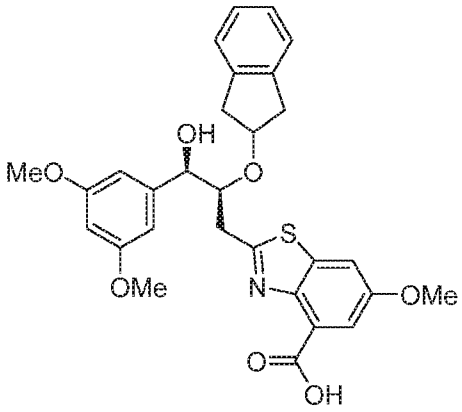
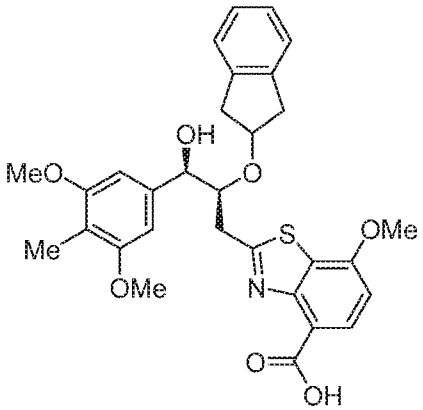
[0070] Provided herein are compounds that are LPA antagonists. In some embodiments, provided is compound selected from Table 1, or a pharmaceutically acceptable salt or solvate thereof:

Table 1

Compound	Structure
101	
102	
103	
104	

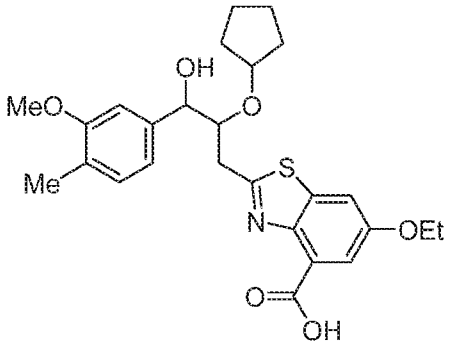
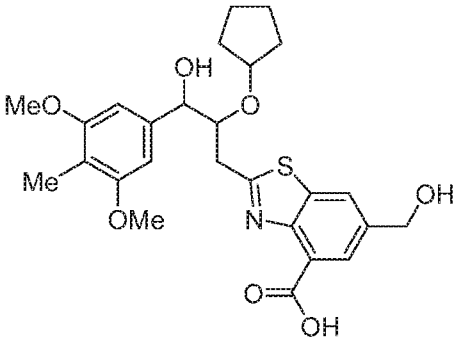
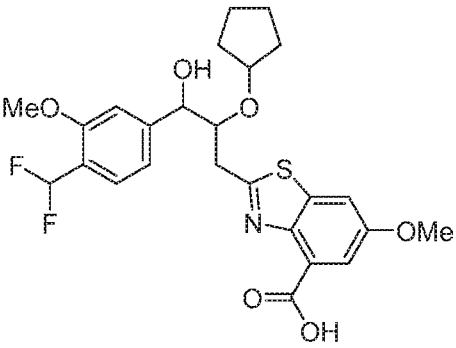
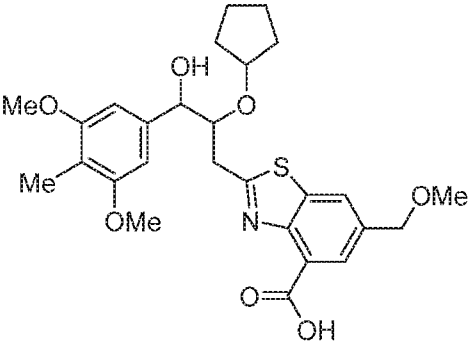
Compound	Structure
105	
106	
107	
108	

Compound	Structure
109	
110	
111	
112	
113	

Compound	Structure
114	
115	
116	
117	

[0071] The compounds 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. Methods known in the art can be used to determine absolute and/or relative configuration, including, but not limited to, chromatography, spectroscopy, X-ray crystallography, and the like. 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, such as those delineated in Table 2. In some embodiments, provided is compound selected from Table 2, or a pharmaceutically acceptable salt, solvate, stereoisomer, or mixture of stereoisomers thereof.

Table 2

Structure	Structure
	
	

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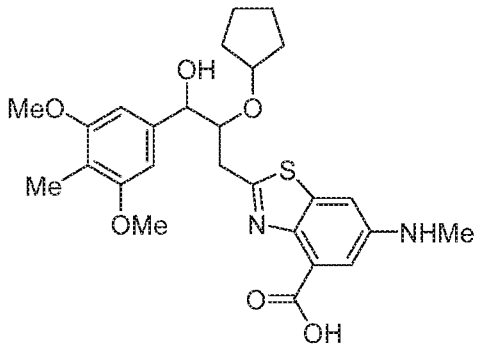
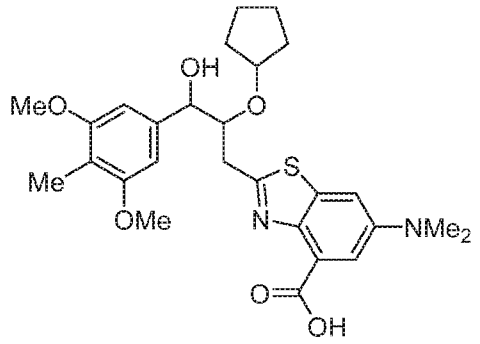
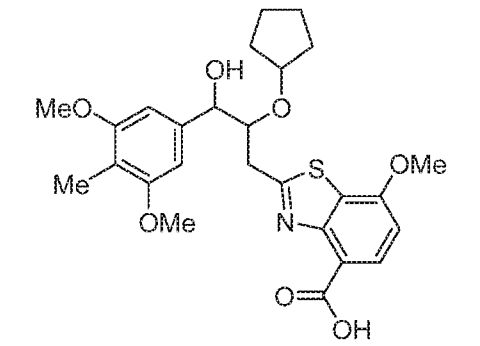
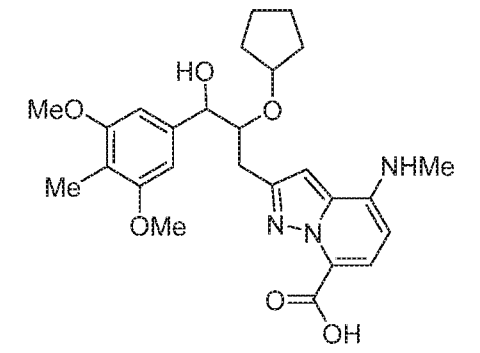

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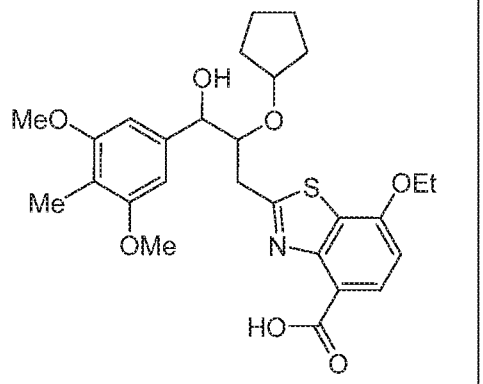
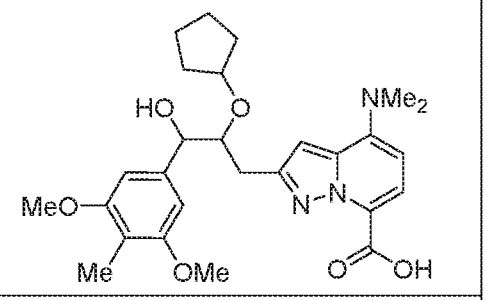
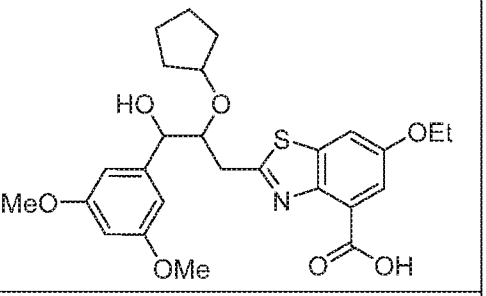
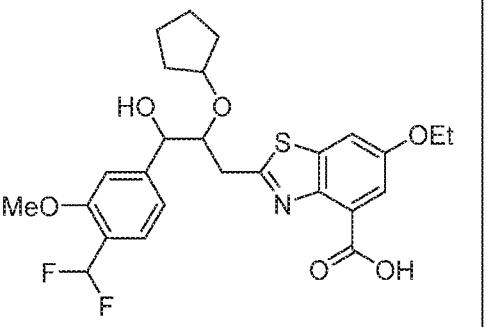
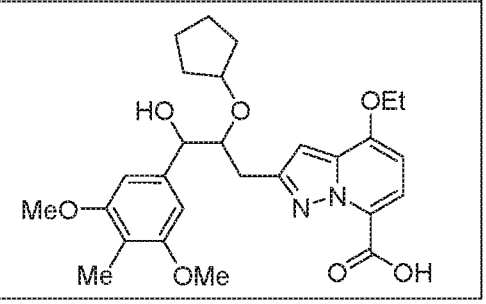
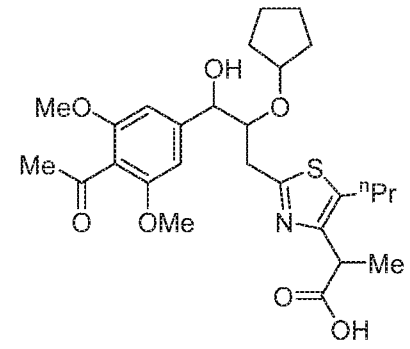
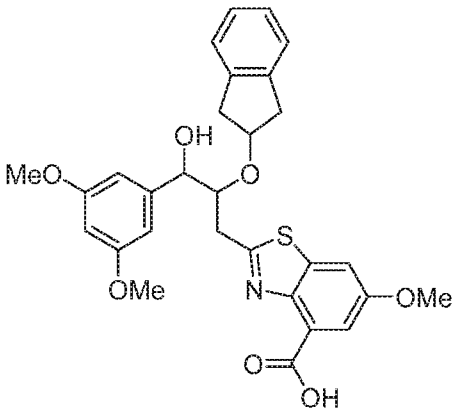
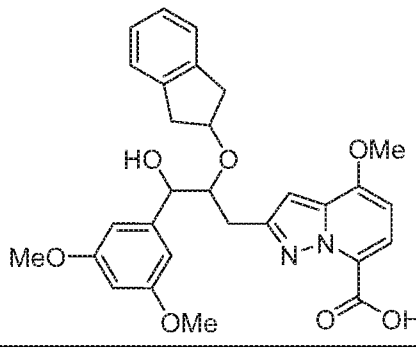
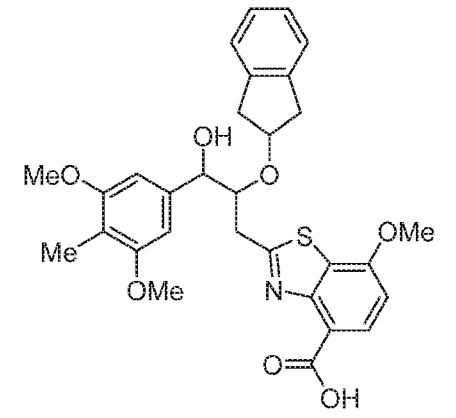






Structure	Structure
	
	

[0072] The compounds disclosed herein include pharmaceutically acceptable salts thereof. In addition, the compounds disclosed herein 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 disclosed herein and/or for separating isomers or enantiomers of the compounds. Non-limiting examples of pharmaceutically acceptable salts of compounds disclosed herein include trifluoroacetic acid salts.

[0073] It will further be appreciated that the compounds disclosed herein 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 disclosed herein 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

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as disclosed herein.

[0078] 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).

[0079] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein.

[0080] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0081] 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 scleroderma, 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.

[0082] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat usual interstitial pneumonia in a subject.

[0083] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0084] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0085] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0086] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0087] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0088] 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.

[0089] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0090] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) is used to treat systemic sclerosis.

[0091] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) is useful to treat or prevent inflammation in a subject. For example, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) can be used in the treatment or prevention of inflammatory/immune disorders in a subject.

[0092] 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.

[0093] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0094] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0095] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0096] 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.

[0097] 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.

[0098] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) as provided herein. In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) can treat asthma (e.g., chronic asthma) in a subject.

[0099] 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., diaphram 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.

[0100] 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.

[0101] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0102] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0103] 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.

[0104] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof).

[0105] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof).

[0106] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) are provided herein.

[0107] 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.

[0108] 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.

[0109] In another example, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) as provided herein is dosed orally p.o. 2 hours to CD-l 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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).

[0116] 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.

[0117] 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.

[0118] 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.

[0119] Improvements in any of the foregoing response criteria are specifically provided by the methods of the present disclosure.

Combination Therapies

[0120] In one embodiment, the compounds disclosed herein may be used in combination with one or more additional therapeutic agent that are being used and/or developed to treat 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....

[0121] 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.

[0122] 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.

[0123] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as disclosed herein.

[0124] 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).

[0125] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein.

[0126] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0127] 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.

[0128] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein, is used to treat usual interstitial pneumonia in a subject.

[0129] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0130] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0131] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0132] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0133] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0134] 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.

[0135] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat one or more symptoms of COVID-19.

[0136] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat chronic obstructive pulmonary disease (COPD).

[0137] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat neuroinflammation.

[0138] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), or a pharmaceutical composition as provided herein is useful to treat multiple sclerosis.

[0139] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0140] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) is used to treat systemic sclerosis.

[0141] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) is useful to treat or prevent inflammation in a subject. For example, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) can be used in the treatment or prevention of inflammatory/immune disorders in a subject.

[0142] 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.

[0143] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0144] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0145] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0146] 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.

[0147] 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.

[0148] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) as provided herein. In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) can treat asthma (e.g., chronic asthma) in a subject.

[0149] 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., diaphram 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.

[0150] 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.

[0151] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0152] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0153] 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.

[0154] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof).

[0155] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof).

[0156] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) are provided herein.

Pharmaceutical Compositions and Modes of Administration

[0157] Compounds provided herein are usually administered in the form of pharmaceutical compositions.

[0158] When employed as pharmaceuticals, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0159] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0160] Further provided herein are pharmaceutical compositions containing a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) with a pharmaceutically acceptable excipient. Pharmaceutical compositions containing a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) as the active ingredient can be prepared by intimately mixing a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0161] 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.

[0162] 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.

[0163] 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).

[0164] In some embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0165] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0166] 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.

[0167] 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.

[0168] In some embodiments, sterile injectable solutions are prepared by incorporating a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0169] 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.

[0170] In some embodiments, suppositories can be prepared by mixing a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0171] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.).

[0172] 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 or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0173] 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 Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0174] 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.

[0175] 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.

[0176] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

[0177] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0178] 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.

[0179] In some embodiments, the dosage for a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0180] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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.

[0181] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) as provided herein is administered as a dosage of about 100 mg/Kg.

[0182] In some embodiments, the foregoing dosages of a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0183] In some embodiments, the period of administration of a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) is administered to a subject for a period followed by a separate period of time where administration of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) is stopped. In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 or solvate thereof, (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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 Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof) followed by a period where administration is stopped is repeated for a determined or undetermined period. 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.

[0184] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0185] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt 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).

[0186] In some embodiments, a compound disclosed herein (e.g., a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt or solvate thereof), is administered by parenteral administration to the subject weekly.

Synthesis of the Compounds

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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).

General Synthesis

[0191] 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

[0192] 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.

[0193] Abbreviations (as used herein):

AcOH	acetic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
CCl_4	carbon tetrachloride

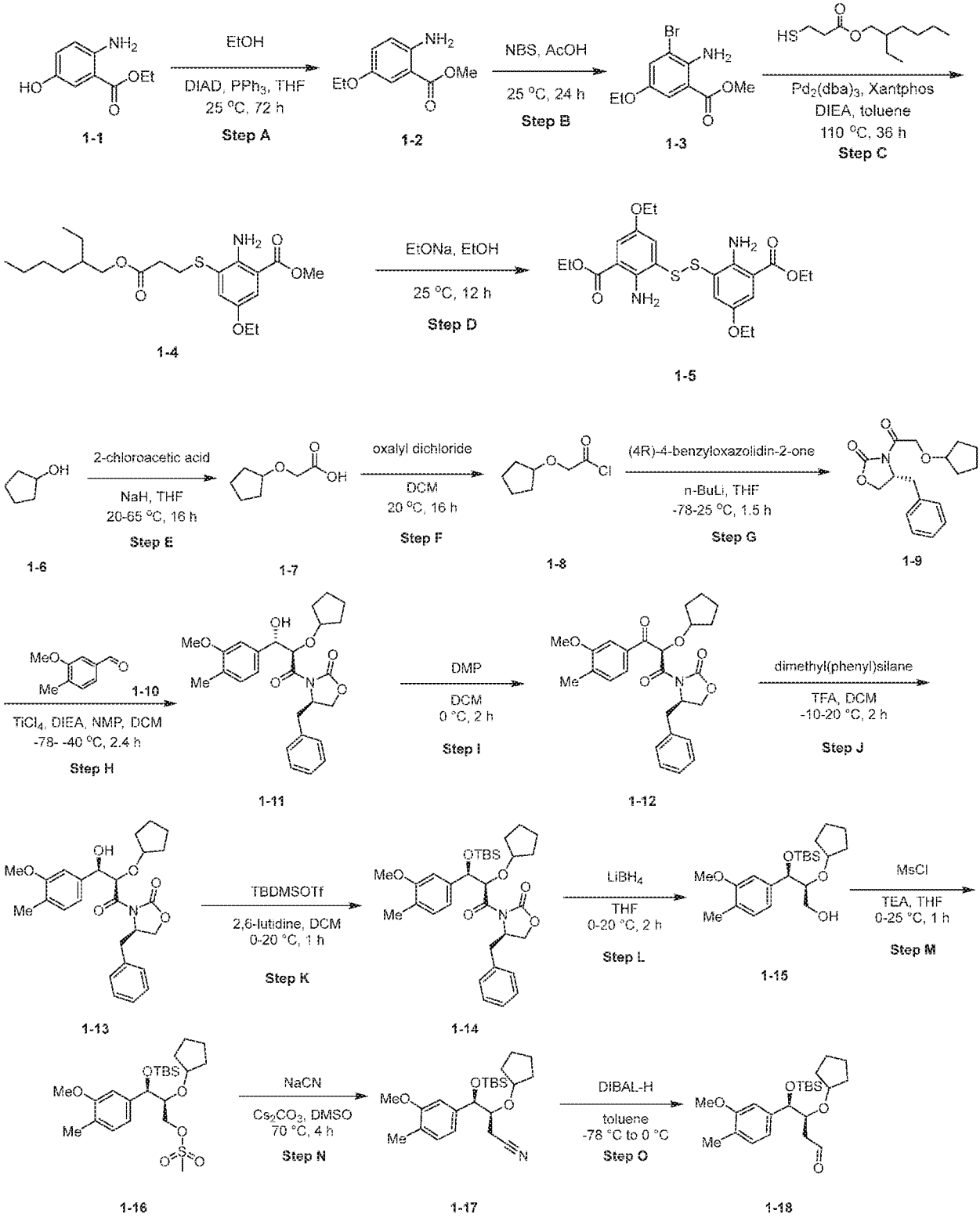
CH_3CN	acetonitrile
CH_2Cl_2 or DCM	dichloromethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIEA or DIPEA	*N*-ethyl-*N,N*-diisopropylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethyl-formamide
DMSO	Dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
h	hour
HCl	hydrochloric acid
H_2O	water
HPLC	High Performance Liquid Chromatography
$[Ir(COD)(OMe)]_2$	(1,5-cyclooctadiene)(methoxy)iridium(I) dimer
K_2CO_3	potassium carbonate
$K_2OsO_4.2H_2O$	potassium osmate
$LiBH_4$	lithium borohydride
MeI	iodomethane
MeOH	methanol
MsCl	methanesulfonyl chloride
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
$NaIO_4$	sodium periodate
NaCN	sodium cyanide
Na_2SO_4	sodium sulfate
NaH	sodium hydride
NaH_2PO_4	sodium phosphate monobasic
NaOH	sodium hydroxide
NBS	bromosuccinimide
n-BuLi	*n*-Butyllithium

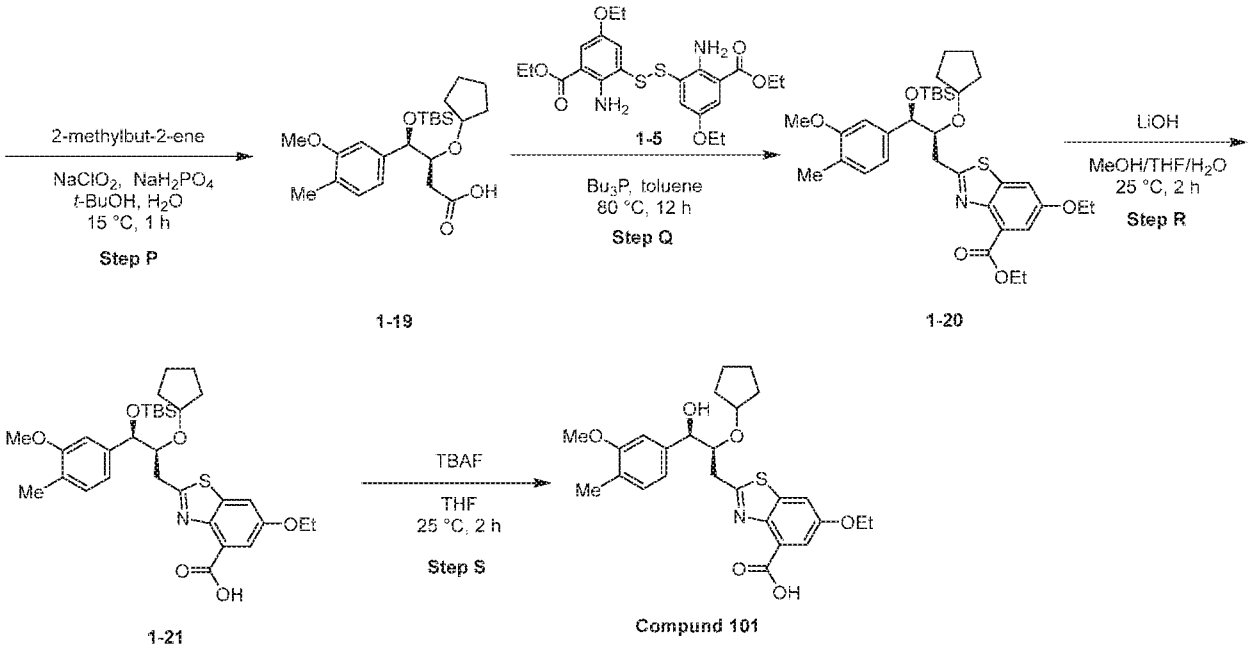
NH_4Cl	ammonium chloride
NMP	1-methyl-pyrrolidin-2-one
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
$Pd(dppf)Cl_2.CH_2Cl_2$	[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) chloride-dichlormethane complex
$Pd(OAc)_2$	palladium (II) Acetate
PE	Petrol ether
PPh_3	triphenylphosphine
Prep.	preparative
PTSA	*p*-toluenesulfonic acid
sat.	saturated
s-Phos	dicyclohexyl-(2',6'-dimethoxybiphenyl-2-yl)-phosphane
t-BuOK	potassium tert-butoxide
t-BuXphos	di-tert-butyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
TMSCl	chlorotrimethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Xphos	dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane

[0194] **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. ^1H 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 spectrometers with electrospray ionization and excepted as otherwise indicated.

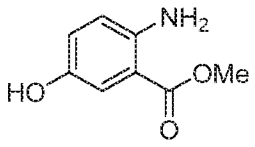
Example A1

2-((2S,3R)-2-(cyclopentyloxy)-3-hydroxy-3-(3-methoxy-4-methylphenyl)propyl)-6-ethoxybenzo[d]thiazole-4-carboxylic acid (Compound 101)



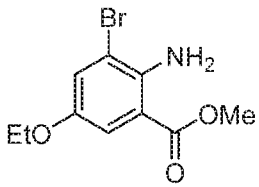


[0195] Step A: methyl 2-amino-5-ethoxybenzoate



[0196] To the solution of methyl 2-amino-5-hydroxy-benzoate (10.0 g, 59.8 mmol), EtOH (5.51 g, 6.99 mL) and PPh_3 (31.4 g, 120 mmol) in THF (150 mL) was added DIAD (24.2 g, 23.3 mL) in dropwise at 25 °C. The resulting reaction mixture was stirred at 25 °C for 72 h. 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 0~15% EtOAc/PE gradient @ 100 mL/min) to afford methyl 2-amino-5-ethoxy-benzoate (10.9 g, 93.0% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (d, J = 2.8 Hz, 1H), 6.97 (dd, J = 8.8, 3.2 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.29 (s, 2H), 3.89 (q, J = 6.8 Hz, 2H), 3.78 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H).

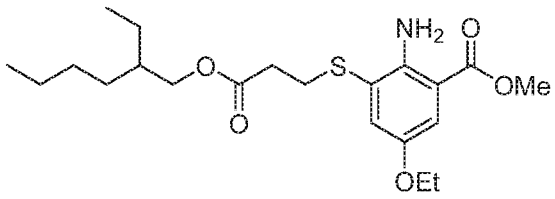
[0197] Step B: methyl 2-amino-3-bromo-5-ethoxybenzoate



[0198] To the solution of methyl 2-amino-5-ethoxy-benzoate (10.9 g, 55.6 mmol) in AcOH (80 mL) was added NBS (9.90 g, 55.6 mmol). The resulting mixture was stirred at 25 °C for 24 h. The reaction

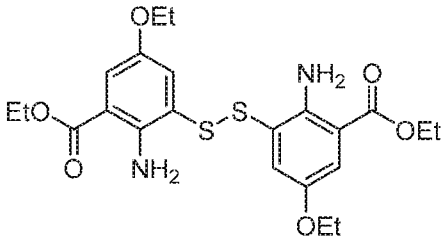
mixture was poured into water (60 mL) and stirred for 10 min. The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/PE gradient @ 100 mL/min) to give methyl 2-amino-3-bromo-5-ethoxy-benzoate (6.65 g, 43.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 2.8 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 5.59 (brs, 2H), 3.87 (q, J = 7.0 Hz, 2H), 3.80 (s, 3H), 1.29 (t, J =7.0 Hz, 3H).

[0199] Step C: methyl 2-amino-5-ethoxy-3-((3-((2-ethylhexyl)oxy)-3-oxopropyl)thio)benzoate



[0200] To the solution of 2-ethylhexyl 3-sulfanylpropanoate (5.30 g, 24.3 mmol) and methyl 2-amino-3-bromo-5-ethoxy-benzoate (6.65 g, 24.3 mmol) in toluene (80 mL) was added $Pd_2(dba)_3$ (1.11 g, 1.21 mmol), Xantphos (1.40 g, 2.43 mmol) and DIEA (7.84 g, 60.7 mmol, 10.6 mL). The mixture was stirred at 110 °C for 36 h. The residue was poured into water (150 mL) and stirred for 10 min. The aqueous phase was extracted with EtOAc (80 mL x 3). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/PE gradient @ 100 mL/min) to afford methyl 2-amino-5-ethoxy-3-[3-(2-ethylhexoxy)-3-oxo-propyl] sulfanyl-benzoate (8.29 g, 83.0% yield).

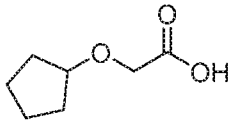
[0201] Step D: methyl 2-amino-5-ethoxy-3-[(3-ethoxy-5-methoxycarbonyl-phenyl)disulfanyl]benzoate



[0202] To the solution of methyl 2-amino-5-ethoxy-3-[2-(2-ethylhexoxy)-2-oxo-ethyl]sulfanyl-benzoate (8.29 g, 20.9 mmol) in EtOH (50 mL) was added EtONa (9.22 g, 27.1 mmol, 20% in EtOH). The reaction mixture was stirred at 25 °C for 12 h. The residue was diluted with water (100 mL), acidified to pH = 6 with 37% HCl, extracted with EtOAc (100 mL x 3). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel

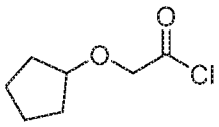
chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/PE gradient @ 100 mL/min) to give methyl 2-amino-5-ethoxy-3-[(3-ethoxy-5-methoxycarbonyl-phenyl)disulfanyl]benzoate (1.09 g, 12.0 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 3.2 Hz, 2H), 6.84 (d, J = 3.2 Hz, 2H), 6.37 (brs, 4H), 4.27 (q, J = 7.2 Hz, 4H), 3.75 (q, J = 6.8 Hz, 4H), 1.32 (t, J = 7.0 Hz, 6H), 1.24 (t, J = 7.0 Hz, 6H).

[0203] Step E: 2-(cyclopentyloxy)acetic acid



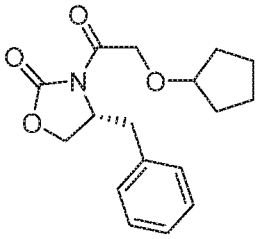
[0204] To a solution of cyclopentanol (3 g, 34.83 mmol) in THF (50 mL) was added NaH (2.79 g, 69.66 mmol, 60% purity) at 0 °C. After being stirred at 60 °C for 30 min, then 2-chloroacetic acid (3.29 g, 34.83 mmol) was added slowly to the reaction mixture at 25 °C. The resulting mixture was stirred at 60 °C for 16 h. After cooling, the reaction mixture was quenched with H_2O (10 mL), diluted with H_2O (50 mL), the *p*H value was adjusted to 5 with 1N HCl. The mixture was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (PE/EtOAc=1/0 to 1/1) to afford 2-(cyclopentoxy)acetic acid (3.7 g, 73% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 4.21 - 4.19 (m, 1H), 3.94 (s, 2H), 1.71 - 1.28 (m, 8H).

[0205] Step F: 2-(cyclopentyloxy)acetyl chloride



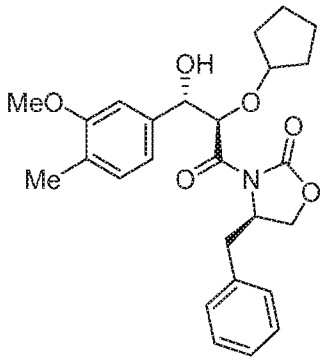
[0206] To a solution of 2-(cyclopentoxy)acetic acid (3.7 g, 25.66 mmol) in DCM (20 mL) was added oxalyl dichloride (4.89 g, 38.50 mmol) and DMF (0.1 mL). Then the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford 2-(cyclopentoxy)acetyl chloride (4.17 g, crude), which was used directly for the next step without further purification.

[0207] Step G: (R)-4-benzyl-3-(2-(cyclopentyloxy)acetyl)oxazolidin-2-one



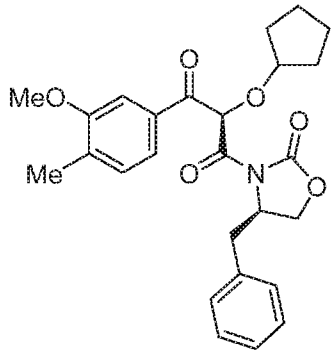
[0208] To a solution of (4R)-4-benzyloxazolidin-2-one (6.82 g, 38.47 mmol) in THF (30 mL) was added *n*-BuLi (14.36 mL, 35.9 mmol, 2.5 M solution in Hexanes) at -78 °C in dropwise under N_2. After addition, a solution of 2-(cyclopentoxy)acetyl chloride (4.17 g, 25.64 mmol) in THF (8 mL) was added to the mixture at -78 °C. The resulting mixture was stirred at 25 °C for 2 h. Then the reaction mixture was quenched by *sat. aq.* NH_4Cl solution (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with water (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (PE/EtOAc=1/0 to 1/1) to afford (4R)-4-benzyl-3-[2-(cyclopentoxy)acetyl]oxazolidin-2-one (2.14 g, 23% yield). LC-MS: m/z 304.1 $(M+H)^+$.

[0209] Step H: (R)-4-benzyl-3-((2R,3S)-2-(cyclopentyloxy)-3-hydroxy-3-(3-methoxy-4-methylphenyl)propanoyl)oxazolidin-2-one



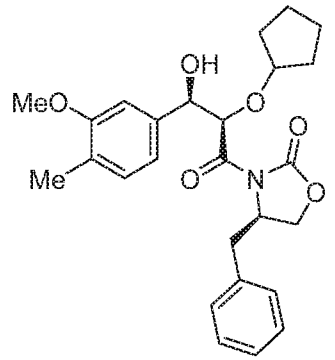
[0210] To a solution of (R)-4-benzyl-3-(2-(cyclopentyloxy)acetyl)oxazolidin-2-one (1.8 g, 5.93 mmol) in DCM (45 mL) was added $TiCl_4$ (683 μL, 6.23 mmol) at -78 ℃ under nitrogen. The mixture was stirred at -78 ℃ for 15 minutes. Then DIEA (2.58 mL, 14.8 mmol) was added in dropwise at -78 ℃. The resulting mixture was stirred at -78 ℃ for 40 minutes. Then NMP (577 μL, 5.93 mmol) was added in dropwise. The reaction mixture was stirred at -78 ℃ for 10 mins under nitrogen. Then 3-methoxy-4-methylbenzaldehyde (980 mg, 6.53 mmol) in dry DCM (10 mL) was added in dropwise. The resulting mixture was stirred at -78 ℃ for 2 h under nitrogen. Then the reaction mixture was quenched with *sat. aq.* NH_4Cl (50 mL), extracted with DCM (60 mL x3). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to get a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~45% EtOAc/PE gradient @ 40 mL/min) to give (R)-4-benzyl-3-((2R,3S)-2-(cyclopentyloxy)-3-hydroxy-3-(3-methoxy-4-methylphenyl)propanoyl)oxazolidin-2-one (2.27 g, 84.4% yield). LC-MS: m/z 476.2 $(M+Na)^+$.

[0211] Step I: (R)-1-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propane-1,3-dione



[0212] At 0 ℃, to the mixture of (R)-4-benzyl-3-((2R,3S)-2-(cyclopentyloxy)-3-hydroxy-3-(3-methoxy-4-methylphenyl)propanoyl)oxazolidin-2-one (2.27 g, 5.01 mmol) in DCM (30 mL) was added Dess-Martin periodinane (4.25 g, 10.0 mmol) in portions. The reaction mixture was stirred at 0 ℃ for 2 h. Then the mixture was quenched with H_2O (50 mL) and DCM (50 mL). The mixture was filtered through a celite and extracted with DCM (50 mL x 2). The organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~35% EtOAc/PE gradient @ 40 mL/min) to give (R)-1-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propane-1,3-dione (2.2 g, 97.4% yield). LC-MS: m/z 474.1 $(M+Na)^+$.

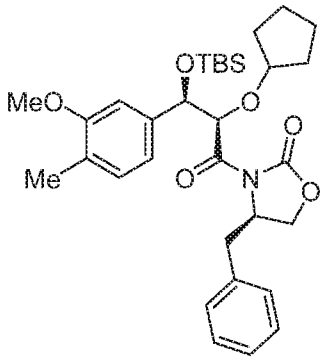
[0213] Step J: (R)-4-benzyl-3-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propanoyl)oxazolidin-2-one



[0214] At -10 ℃, to the mixture of (R)-1-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propane-1,3-dione (2.2 g, 4.87 mmol) in TFA (21.7 mL) and DCM (22 mL) was added dimethyl(phenyl)silane (2.27 mL, 14.6 mmol) in dropwise. The reaction mixture was stirred at -10 ℃ for 2 h. The solution was poured into *sat. aq.* $NaHCO_3$ (200 mL), extracted with DCM (30 mL x 3). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g Sepa Flash® Silica Flash Column, Eluent of

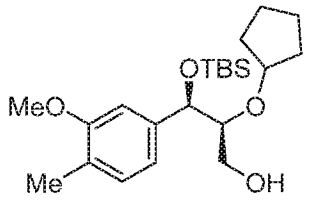
0~50% EtOAc/PE gradient @ 40 mL/min) to give (R)-4-benzyl-3-((2R,3R)-2-(cyclopentyloxy)-3-hydroxy-3-(3-methoxy-4-methylphenyl)propanoyl)oxazolidin-2-one (1.85 g, 83.7% yield). LC-MS: m/z 476.1 $(M+Na)^+$.

[0215] Step K: (R)-4-benzyl-3-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propanoyl)oxazolidin-2-one



[0216] To the mixture of (R)-4-benzyl-3-((2R,3R)-2-(cyclopentyloxy)-3-hydroxy-3-(3-methoxy-4-methylphenyl)propanoyl)oxazolidin-2-one (1.85 g, 4.08 mmol) in DCM (15 mL) and 2,6-dimethylpyridine (950 μL, 8.16 mmol) was added [tert-butyl(dimethyl)silyl] trifluoromethanesulfonate (1.88 mL, 8.16 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 2 h. Then the mixture was quenched with H_2O (50 mL), extracted with DCM (50 mL x 3). The organic layers were washed with H_2O (50 mL x 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~10% EtOAc/PE gradient @ 35 mL/min) to give (4R)-4-benzyl-3-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-methyl-phenyl)propanoyl]oxazolidin-2-one (2.2 g, 95.0% yield).

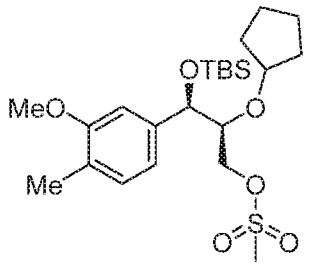
[0217] Step L: (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propan-1-ol



[0218] At 0 °C, to the mixture of $LiBH_4$ (9.69 mL, 38.76 mmol, 4 M solution in THF) in THF (10 mL) was added H_2O (15.4 mg, 852 μmol) dropwise under N_2. The mixture was stirred at 0 °C for 0.5 h. Then a solution of (*R*)-4-benzyl-3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-

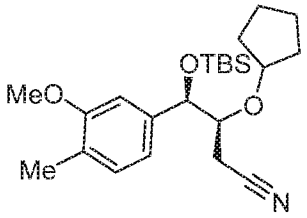
methylphenyl)propanoyl)oxazolidin-2-one (2.2 g, 3.87 mmol) in THF (20 mL) was added in dropwise. The reaction mixture was warmed up to 15 °C and stirred at 15 °C for 16 h. The reaction mixture was carefully neutralized with 1 M *aq*. HCl solution, extracted with EtOAc (30 mL x 3). The organic layers 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®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~10% EtOAc/PE gradient @ 40 mL/min) to give (2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propan-1-ol (1.26 g, 82.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 7.2 Hz, 1H), 6.85 (s, 1H), 6.79 (d, J = 7.6 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 3.82 (s, 3H), 3.81 - 3.70 (m, 3H), 3.36 - 3.35 (m, 1H), 2.20 (s, 3H), 1.58-1.26 (m, 8H), 0.89 (s, 9H), 0.05 (s, 3H), -0.16 (s, 3H).

[0219] Step M: (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propyl methanesulfonate



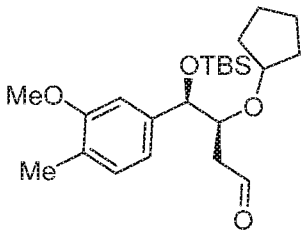
[0220] To the mixture of (2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propan-1-ol (1.26 g, 3.19 mmol) in DCM (20 mL) and TEA (667 μL, 4.79 mmol) was added MsCl (439 mg, 3.83 mmol, 297 μL) in dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. The mixture was quenched with *sat. aq*. $NaHCO_3$ (50 mL), extracted with DCM (20 mL x 3). The organic layers were washed with 0.5N HCl (20 mL x 2), brine (20 mL x 2), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~15% EtOAc/PE gradient @ 35 mL/min) to give (2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propyl methanesulfonate (1.42 g, 94.1% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 6.79 - 6.76 (m, 1H), 4.65 (d, J = 5.6 Hz, 1H), 4.41 - 4.27 (m, 2H), 3.82 (s, 4H), 3.57 - 3.56 (m, 1H), 2.99 (s, 3H), 2.20 (s, 3H), 1.61 -1.30 (m, 8H), 0.89 (s, 9H), 0.07 (s, 3H), -0.14 (s, 3H).

[0221] Step N: (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3-methoxy-4-methylphenyl)butanenitrile



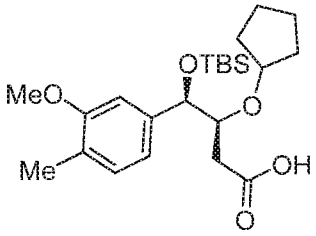
[0222] To a solution of [(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-methyl-phenyl)propyl] methanesulfonate (6.0 g, 12.69 mmol) in DMSO (60 mL) was added NaCN (3.11 g, 63.46 mmol). The mixture was stirred at 85 ℃ for 3 h. After cooling, the mixture was quenched with H_2O (60 mL), extracted with EtOAc (60 mL x 2). The combined organic layers were 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 (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3-methoxy-4-methylphenyl) butanenitrile (4 g, 78.1% yield). LC-MS: m/z 426.2 $(M+Na)^+$.

[0223] Step O: (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3-methoxy-4-methylphenyl)butanal



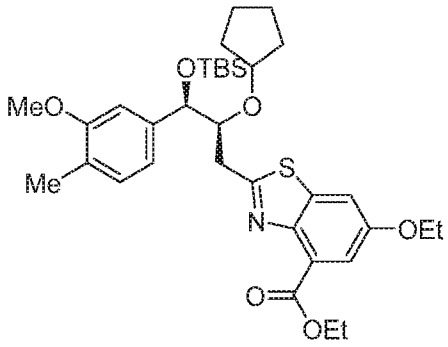
[0224] To a solution of (3S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-(cyclopentoxy)-4-(3-methoxy-4-methyl-phenyl)butanenitrile (4.0 g, 9.91 mmol) in toluene (50 mL) was added DIBAL-H (19.82 mL, 19.82mmol) at -78 ℃. The reaction mixture was stirred at 0 ℃ for 1 h. Then the mixture was quenched with potassium sodium tartaric solution (50 mL), extracted with EtOAc (50mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford crude (3S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-(cyclopentoxy)-4-(3-methoxy-4-methyl-phenyl)butanal (4.0 g, 99.2% yield), which used for next step without further purification.

[0225] Step P: (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3-methoxy-4-methylphenyl)butanoic acid



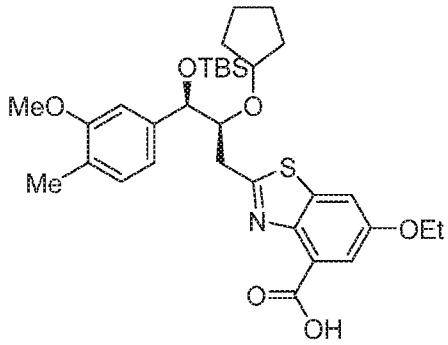
[0226] To a solution of (3S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-(cyclopentoxy)-4-(3-methoxy-4-methyl-phenyl)butanal (4.0 g, 9.84 mmol) in *t*-BuOH (40 mL) and H_2O (10 mL) was added NaH_2PO_4 (1.18 g, 9.84 mmol), sodium chlorite (3.20 g, 35.41 mmol) and 2-methylbut-2-ene (3.10 g, 44.27 mmol). The reaction mixture was stirred at 25 ℃ for 1 h. Then the mixture was quenched with H_2O (60 mL), extracted with EtOAc (60 mL x 2). The combined organic layers were 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 (3S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-(cyclopentoxy)-4-(3-methoxy-4-methyl-phenyl)butanoic acid (1.6 g, 38.5% yield). LC-MS: m/z 445.1 $(M+Na)^+$.

[0227] Step Q: ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propyl)-6-ethoxybenzo[d]thiazole-4-carboxylate



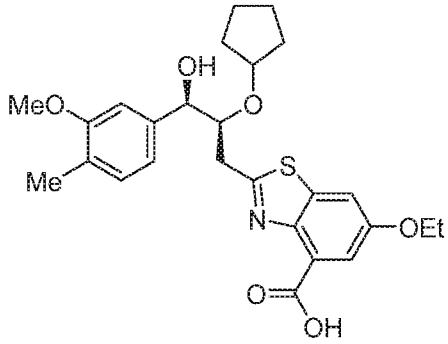
[0228] To a solution of (3S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-(cyclopentoxy)-4-(3-methoxy-4-methyl-phenyl)butanoic acid (300 mg, 709.84 μmol) and ethyl 2-amino-3-[(2-amino-5-ethoxy-3-ethoxycarbonyl-phenyl)disulfanyl]-5-ethoxy-benzoate (341 mg, 709.84 μmol) in toluene (10 mL) was added tributylphosphane (430 mg, 2.13 mmol). The reaction mixture was stirred at 80 ℃ for 12 h. The mixture was quenched with H_2O (30 mL), extracted with EtOAc (30 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 silica gel column (PE/EtOAc = 10/1) to afford compound ethyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-methyl-phenyl)propyl]-6-ethoxy-1,3-benzothiazole-4-carboxylate (110 mg, 24.7% yield). LC-MS: m/z 628.3 $(M+H)^+$.

[0229] Step R: 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-methylphenyl)propyl)-6-ethoxybenzo[d]thiazole-4-carboxylic acid



[0230] To a solution of ethyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-methyl-phenyl)propyl]-6-ethoxy-1,3-benzothiazole-4-carboxylate (110 mg, 175.19 μmol) in THF (2 mL), EtOH (2 mL) and H_2O (2 mL) was added $LiOH·H_2O$ (37 mg, 875.93 μmol). The mixture was stirred at 25 ℃ for 1 h. The reaction mixture was adjusted to pH = 4 with 1 N HCl, extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-methyl-phenyl)propyl]-6-ethoxy-1,3-benzothiazole-4-carboxylic acid (100 mg, 95.1% yield), which used for next step without further purification. LC-MS: m/z 600.3 $(M+H)^+$.

[0231] Step S: 2-((2S,3R)-2-(cyclopentyloxy)-3-hydroxy-3-(3-methoxy-4-methylphenyl)propyl)-6-ethoxybenzo[d]thiazole-4-carboxylic acid **(Compound 101)**

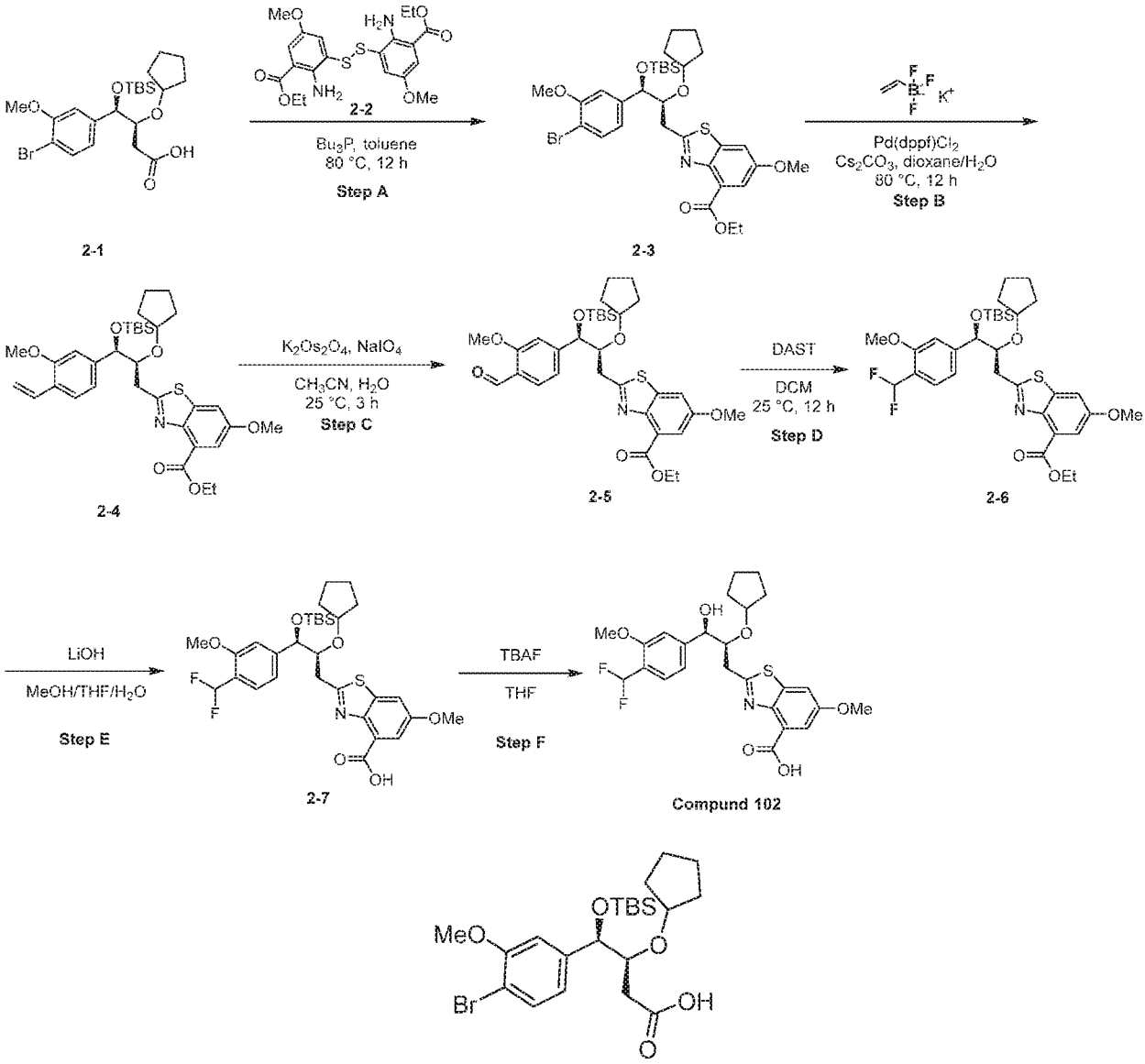


[0232] To a solution of 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-methyl-phenyl)propyl]-6-ethoxy-1,3-benzothiazole-4-carboxylic acid (100 mg, 166.71 μmol) in THF (5 mL) was added TBAF (1.67 mL, 1.67 mmol). The mixture was stirred at 25 ℃ for 1 h. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (30 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 *prep*. HPLC (Column: Welch Xtimate C18 150*30 mm*5 μm; Mobile phase A: [water

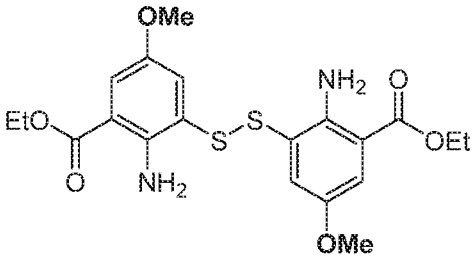
(0.1% HCOOH)], Mobile Phase B: CH_3CN; Gradient: 55% B% to 85% B% in 7 min) to afford 2-[(2S,3R)-2-(cyclopentoxy)-3-hydroxy-3-(3-methoxy-4-methyl-phenyl)propyl]-6-ethoxy-1,3-benzothiazole-4-carboxylic acid (30 mg, 36.5% yield). LC-MS: m/z 486.1 $(M+Na)^+$. ^1H NMR (400MHz, CD_3OD) δ 7.74 (d, J = 4.0, 1H), 7.71 (d, J = 4.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 4.69 (d, J = 8.0 Hz, 1H), 4.15 (q, J = 8.0 Hz, 2H), 3.98 - 3.88 (m, 2H), 3.84 (s, 3H), 3.43 (d, J = 4.0 Hz, 2H), 2.15 (s, 3H), 1.54 - 1.40 (m, 8H), 1.38 - 1.28 (m, 3H).

Example A2

2-((2S,3R)-2-(cyclopentyloxy)-3-(4-(difluoromethyl)-3-methoxyphenyl)-3-hydroxypropyl)-6-methoxybenzo[d]thiazole-4-carboxylic acid (Compound 102)

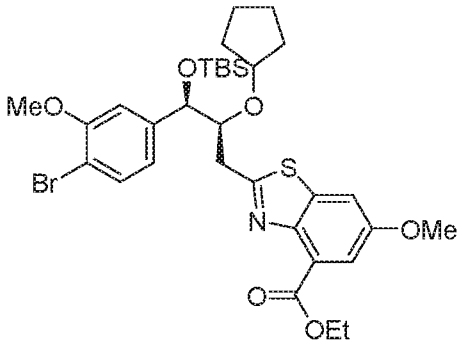


[0233] (3S,4R)-4-(4-bromo-3-methoxyphenyl)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)butanoic acid (**2-1**) was synthesized according to the procedures described for the preparation of Example **A1** (step **H** to step **P** in Scheme **1**) by using 4-bromo-3-methoxy-benzaldehyde in step **H**.



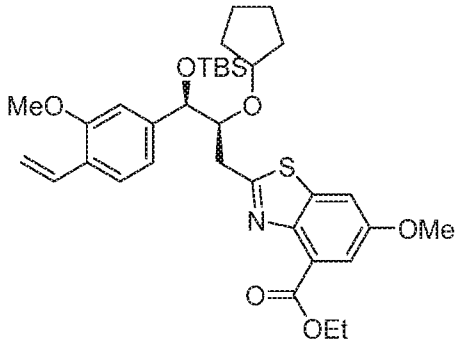
[0234] Ethyl 2-amino-3-[(2-amino-3-ethoxycarbonyl-5-methoxy-phenyl)disulfanyl]-5-methoxy-benzoate (**2-2**) was synthesized according to the procedures described for the preparation of Example **A1** (step **C** to step **D** in Scheme **1**) by using methyl 2-amino-3-bromo-5-methoxybenzoate in step **C**. ^{1}H NMR (400 MHz, CDCl3) δ 7.53 (d, J = 3.2 Hz, 2H), 6.88 (d, J = 3.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 4H), 3.63 (s, 6H), 1.40 (t, J = 7.2 Hz, 6H).

[0235] Step A: ethyl 2-((2S,3R)-3-(4-bromo-3-methoxyphenyl)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)propyl)-6-methoxybenzo[d]thiazole-4-carboxylate



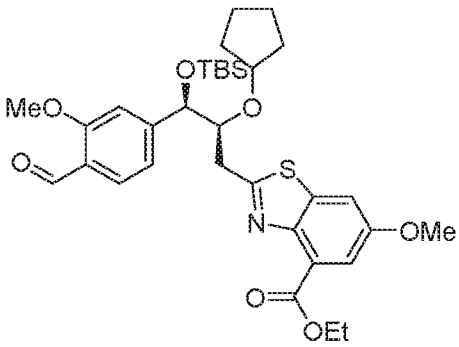
[0236] To a solution of (3S,4R)-4-(4-bromo-3-methoxyphenyl)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)butanoic acid (850 mg, 1.74 mmol) and ethyl 2-amino-3-[(2-amino-3-ethoxycarbonyl-phenyl) disulfanyl]benzoate (789 mg, 1.74 mmol) in toluene (10 mL) was added tributylphosphane (1.06 g, 5.23 mmol). The reaction mixture was stirred at 80 ℃ for 12 h. After cooling, the mixture was quenched with H_2O (30 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were 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 ethyl 2-[(2S,3R)-3-(4-bromo-3-methoxy-phenyl)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)propyl]-6-methoxy-1,3-benzothiazole-4-carboxylate (500 mg, 42.2% yield) as yellow oil. LC-MS: m/z 680.1 $(M+H)^+$.

[0237] Step B: ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3-methoxy-4-vinylphenyl)propyl)-6-methoxybenzo[d]thiazole-4-carboxylate



[0238] To a solution of ethyl 2-[(2S,3R)-3-(4-bromo-3-methoxy-phenyl)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)propyl]-6-methoxy-1,3-benzothiazole-4-carboxylate (330 mg, 486.19 μmol) in H_2O (2 mL) and dioxane (8 mL) was added $Pd(dppf)Cl_2$ (36 mg, 48.62 μmol), potassium ethenyltrifluoroborate (130 mg, 972.38 μmol) and Cs_2CO_3 (475 mg, 1.46 mmol). The mixture was stirred at 80 ℃ for 12 h. After cooling, the mixture was diluted with H_2O (30 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were 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 ethyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-vinyl-phenyl)propyl]-6-methoxy-1,3-benzothiazole-4-carboxylate (240 mg, 78.8% yield). LC-MS: m/z 626.2 $(M+H)^+$.

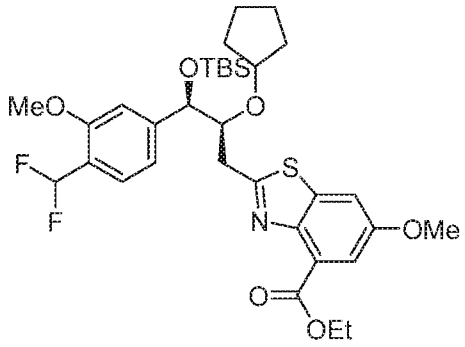
[0239] Step C: ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(4-formyl-3-methoxyphenyl)propyl)-6-methoxybenzo[d]thiazole-4-carboxylate



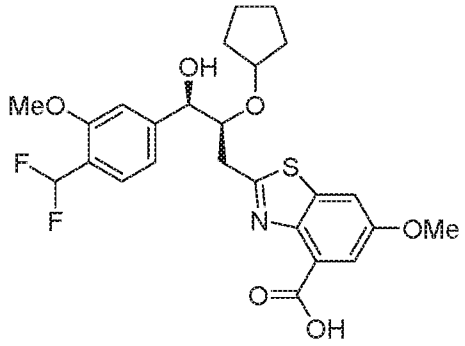
[0240] To a solution of ethyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3-methoxy-4-vinyl-phenyl)propyl]-6-methoxy-1,3-benzothiazole-4-carboxylate (200 mg, 319.55 μmol) in THF (3 mL) and H_2O (3 mL) was added $NaIO_4$ (273 mg, 1.28 mmol) and $K_2OsO_4.2H_2O$ (1 mg, 1.92 μmol). The reaction mixture was stirred at 25 ℃ for 3 h. The mixture was quenched with H_2O (30 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were 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 ethyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(4-formyl-3-methoxy-phenyl)propyl]-6-methoxy-1,3-benzothiazole-4-carboxylate (150 mg, 74.7% yield). LC-MS: m/z 628.3 $(M+H)^+$.

[0241] Step D: ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(4-(difluoromethyl)-3-methoxyphenyl)propyl)-6-methoxybenzo[d]thiazole-4-carboxylate



[0242] To a solution of ethyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(4-formyl-3-methoxy-phenyl)propyl]-6-methoxy-1,3-benzothiazole-4-carboxylate (150 mg, 238.91 μmol) in DCM (3 mL) was added DAST (192.55 mg, 1.19 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. The mixture was quenched with *sat. aq.* $NaHCO_3$ (30 mL), extracted with DCM (30 mL x 2). The combined organic layers were 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 ethyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-[4-(difluoromethyl)-3-methoxy-phenyl]propyl]-6-methoxy-1,3-benzothiazole-4-carboxylate (70 mg, 45.1% yield). LC-MS: m/z 672.2 $(M+Na)^+$.

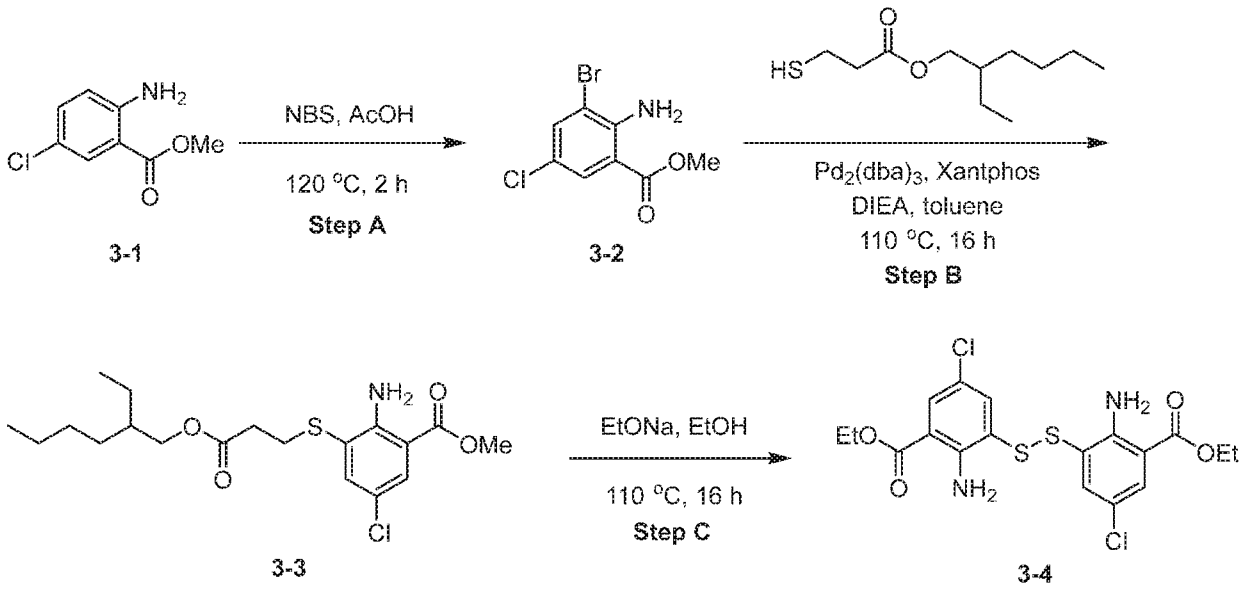


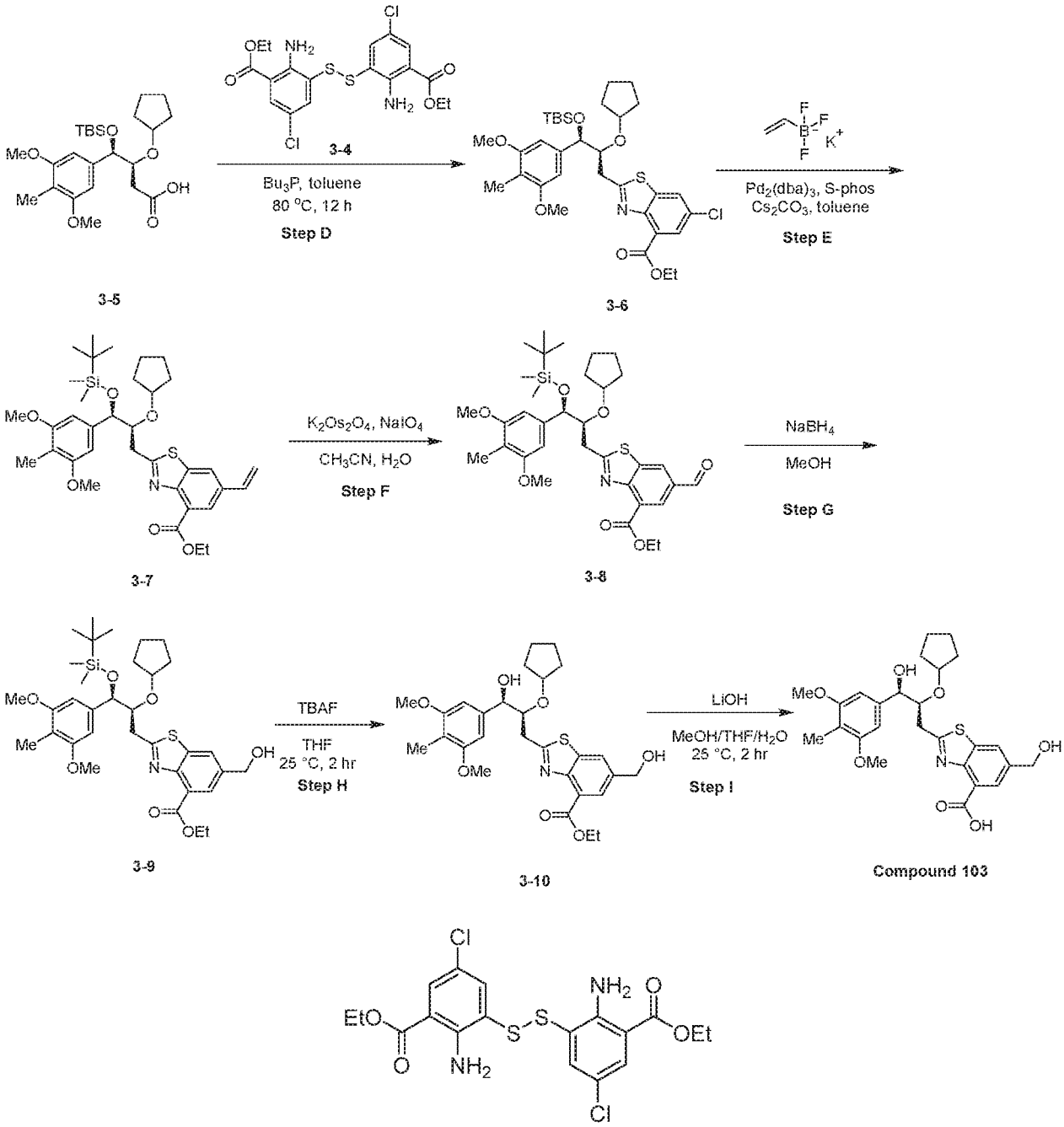
[0243] 2-((2S,3R)-2-(cyclopentyloxy)-3-(4-(difluoromethyl)-3-methoxyphenyl)-3-hydroxypropyl)-6-methoxybenzo[d]thiazole-4-carboxylic acid **(compound 102)** was synthesized according to the procedures described for the preparation of Example **A1** (step **R** to step **S** in Scheme 1) by using ethyl 2-

((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(4-(difluoromethyl)-3-methoxyphenyl)propyl)-6-methoxybenzo[d]thiazole-4-carboxylate in step **R**. LC-MS: m/z 508.0 $(M+H)^+$. ^1H NMR (400MHz, CD_3OD) δ 7.75 - 7.72 (m, 1H), 7.71 - 7.68 (m, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.06 - 6.76 (m, 1H), 6.92 (t, J = 55.6 Hz, 1H), 4.74 (d, J = 4.0 Hz, 1H), 3.99 - 3.93 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.52 - 3.39 (m, 2H), 1.58 - 1.45 (m, 3H), 1.42 - 1.30 (m, 5H).

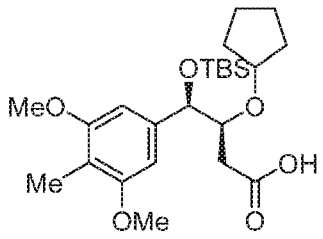
Example A3

2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(hydroxymethyl)benzo[d]thiazole-4-carboxylic acid (Compound 103)

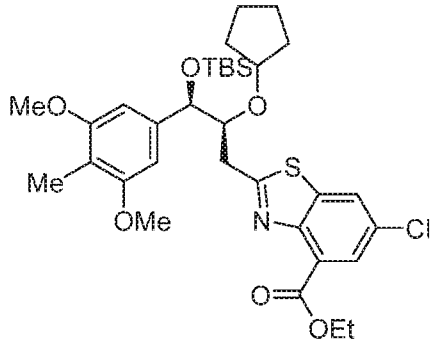




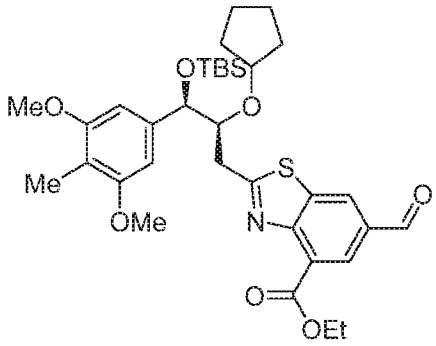
[0244] Diethyl 3,3'-disulfanediylbis(2-amino-5-chlorobenzoate) (**3-4**) was synthesized according to the procedures described for the preparation of **Example A1** (step **B** to step **D** in Scheme **1**) by using methyl 2-amino-5-chloro-benzoate in step **B**. LC-MS: m/z 460.9 $(M+H)^+$.



[0245] (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3,5-dimethoxy-4-methylphenyl)butanoic acid (**3-5**) was synthesized according to the procedures described for the preparation of **Example A1** (step **H** to step **P** in Scheme **1**) by using 3,5-dimethoxy-4-methylbenzene-1-carbaldehyde in step **H**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 2H), 4.71 - 4.70 (m ,1H), 3.98 - 3.95 (m, 1H), 3.84 - 3.77 (m, 7H), 2.60 - 2.57 (m, 2H), 2.06 (s, 3H), 1.67 - 1.26 (m, 8H), 0.91 (s, 9H), 0.07 (s, 3H), -0.11 (s, 3H).

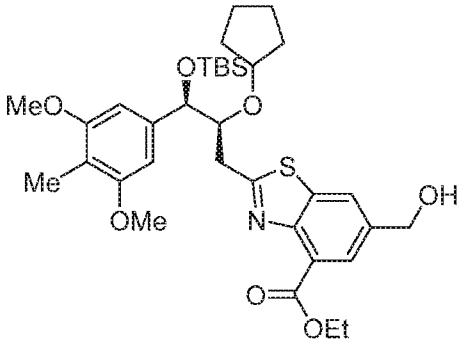


[0246] Ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-6-chlorobenzo[d]thiazole-4-carboxylate (**3-6**) was synthesized according to the procedures described for the preparation of **Example A1** (step **Q** in Scheme **1**) by diethyl 3,3'-disulfanediylbis(2-amino-5-chlorobenzoate) (**3-4**) and (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3,5-dimethoxy-4-methylphenyl)butanoic acid (**3-5**) in step **Q**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.99 (m, 2H), 6.55 (s, 2H), 4.75 - 4.74 (m, 1H), 4.49 - 4.44 (m, 2H), 3.94 - 3.92 (m, 1H), 3.83 - 3.82 (m, 7H), 3.46 - 3.35 (m, 2H), 2.05 (s, 3H), 1.51 - 1.32 (m, 11H), 0.91 (s, 9H), 0.07 (s, 3H), -0.12 (s, 3H).

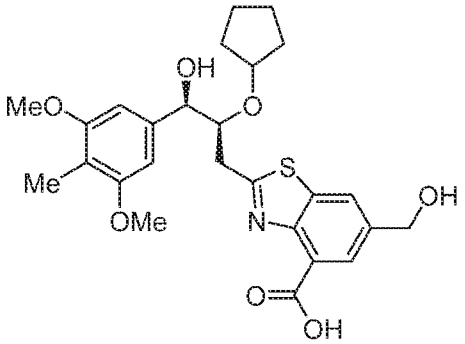


[0247] Ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-6-formylbenzo[d]thiazole-4-carboxylate (**3-8**) was synthesized according to the procedures described for the preparation of **Example A2** (step **B** to step **C** in Scheme **2**) by using ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl) -6-chlorobenzo[d]thiazole-4-carboxylate (**3-6**). LC-MS: m/z 642.2 $(M+H)^+$.

[0248] Step G: ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-6-(hydroxymethyl)benzo[d]thiazole-4-carboxylate



[0249] To a solution of ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-6-formylbenzo[d] thiazole-4-carboxylate (30 mg, 46.78 μmol) in MeOH (1 mL) was added $NaBH_4$ (5.30 mg, 140.21 μmol). The reaction mixture was stirred at 25 °C for 3 h. Then the mixture was quenched with *sat.aq.* NH_4Cl solution (10 mL), extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na2SO4, filtered and concentrated to give ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl) propyl)-6-(hydroxymethyl)benzo[d]thiazole-4-carboxylate (20 mg, 66% yield). LC-MS: m/z 644.3 $(M+H)^+$.

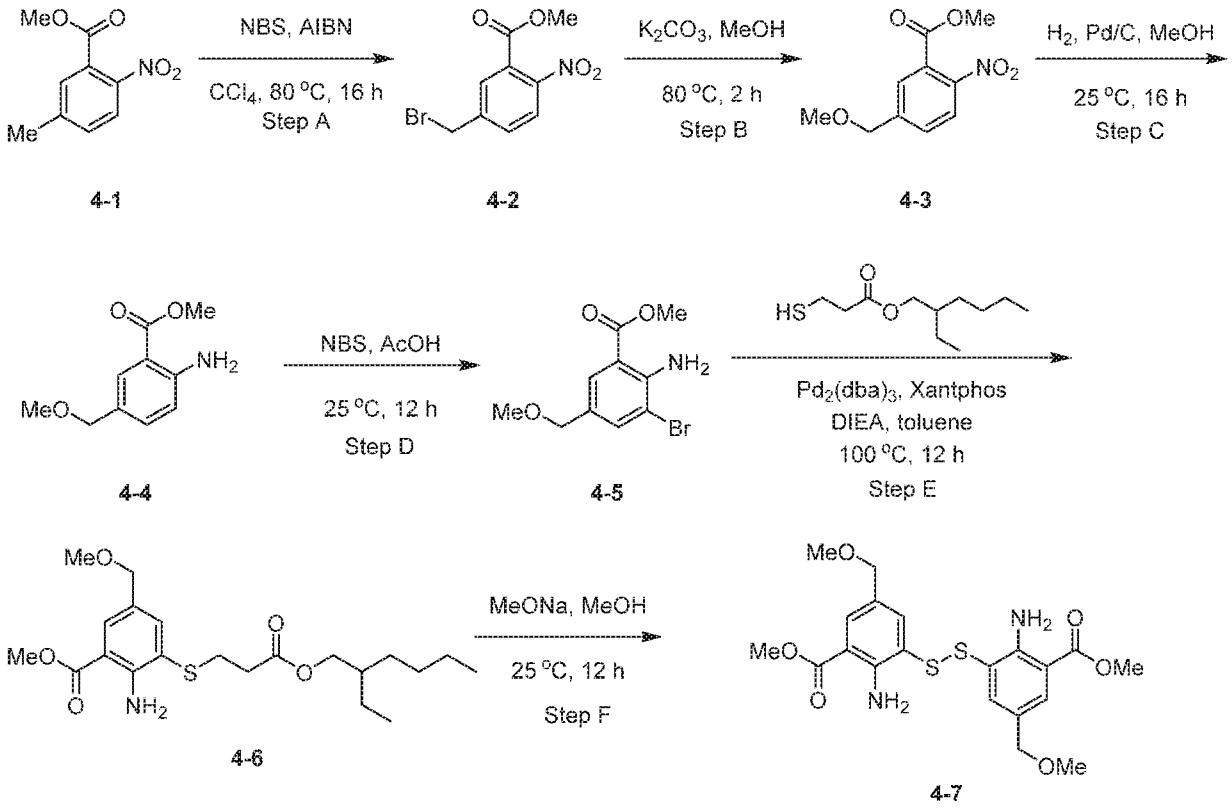


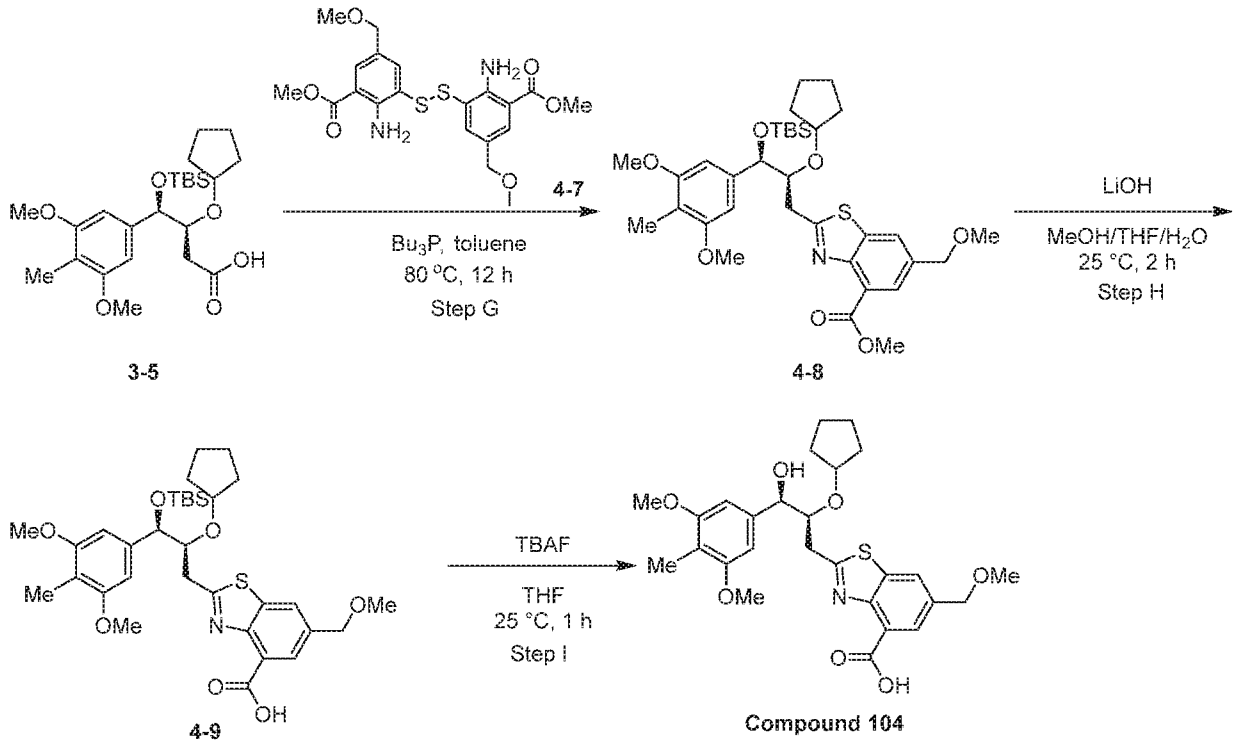
[0250] 2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(hydroxymethyl)benzo[d]thiazole-4-carboxylic acid (**Compound 103**) was synthesized according to the procedures described for the preparation of **Example A1** (step **S** and step **R** in Scheme **1**) by using ethyl

2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl) propyl)-6-(hydroxymethyl)benzo[d]thiazole-4-carboxylate (**3-9**) in step **S**. LC-MS: m/z 502.3 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.94 (s, 1H), 6.64 (s, 2H), 4.75 (s, 1H), 4.61 (s, 2H), 3.97 - 3.93 (m, 1H), 3.86 - 3.79 (m, 1H), 3.79 (s, 6H), 3.45 - 3.43 (m, 2H), 3.30-3.29 (m, 1H), 1.99 (s, 3H), 1.42 - 1.32 (m, 8H).

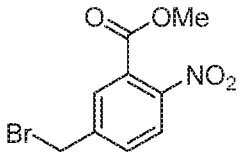
Example A4

2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(methoxymethyl)benzo[d]thiazole-4-carboxylic acid (Compound 104)



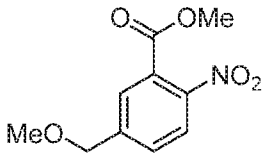


[0251] Step A: methyl 5-(bromomethyl)-2-nitrobenzoate



[0252] To a solution of methyl 5-methyl-2-nitro-benzoate (23.5 g, 120.41 mmol) in CCl_4 (200 mL) was added AIBN (1.98 g, 12.04 mmol) and NBS (32.15 g, 180.61 mmol). The reaction mixture was stirred at 80 °C for 16 h. After cooling, the reaction was diluted with H_2O (300 mL), extracted with DCM (300 mL x 3). The combined organics were concentrated under reduced pressure to give a residue. The residue was purified by column (PE/EtOAc = 7/1) to give methyl 5-(bromomethyl)-2-nitrobenzoate (19.12 g, 38.6% yield).

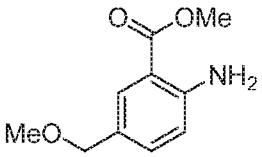
[0253] Step B: methyl 5-(methoxymethyl)-2-nitrobenzoate



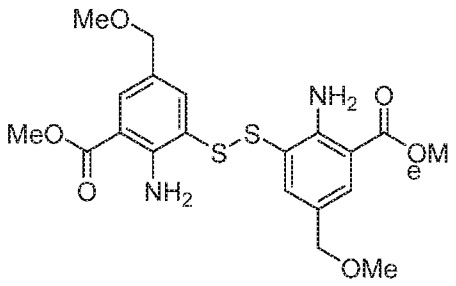
[0254] To a solution of methyl 5-(bromomethyl)-2-nitrobenzoate (19.12 g, 69.77 mmol) in MeOH (180 mL) was added K_2CO_3 (9.64 g, 69.77 mmol). The mixture was stirred at 80 °C for 2 h. The reaction was

diluted with H_2O (300 mL), extracted with EtOAc (300 mL x 3). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (PE/EtOAc = 5/1) to give the methyl 5-(methoxymethyl)-2-nitrobenzoate (10.52 g, 66.9% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 1.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 4.48 (s, 2H), 3.86 (s, 3H), 3.38 (s, 3H).

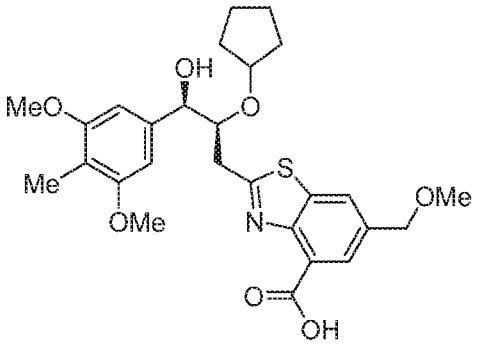
[0255] Step C: methyl 2-amino-5-(methoxymethyl)benzoate



[0256] To a solution of methyl 5-(methoxymethyl)-2-nitro-benzoate (7.52 g, 33.39 mmol) in EtOAc (100 mL) was added 10% Pd/C (2.6 g) under N_2 and the mixture was degassed and purged with N_2 for 3 times. Then the mixture was degassed and purged with H_2 for 3 times. The mixture was stirred at 25 °C under H_2 (45 psi) for 16 h. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (PE/EtOAc = 6/1) to give the methyl 2-amino-5-(methoxymethyl)benzoate (5.85 g, 79.6% yield). LC-MS: m/z 195.8 $(M+H)^+$.



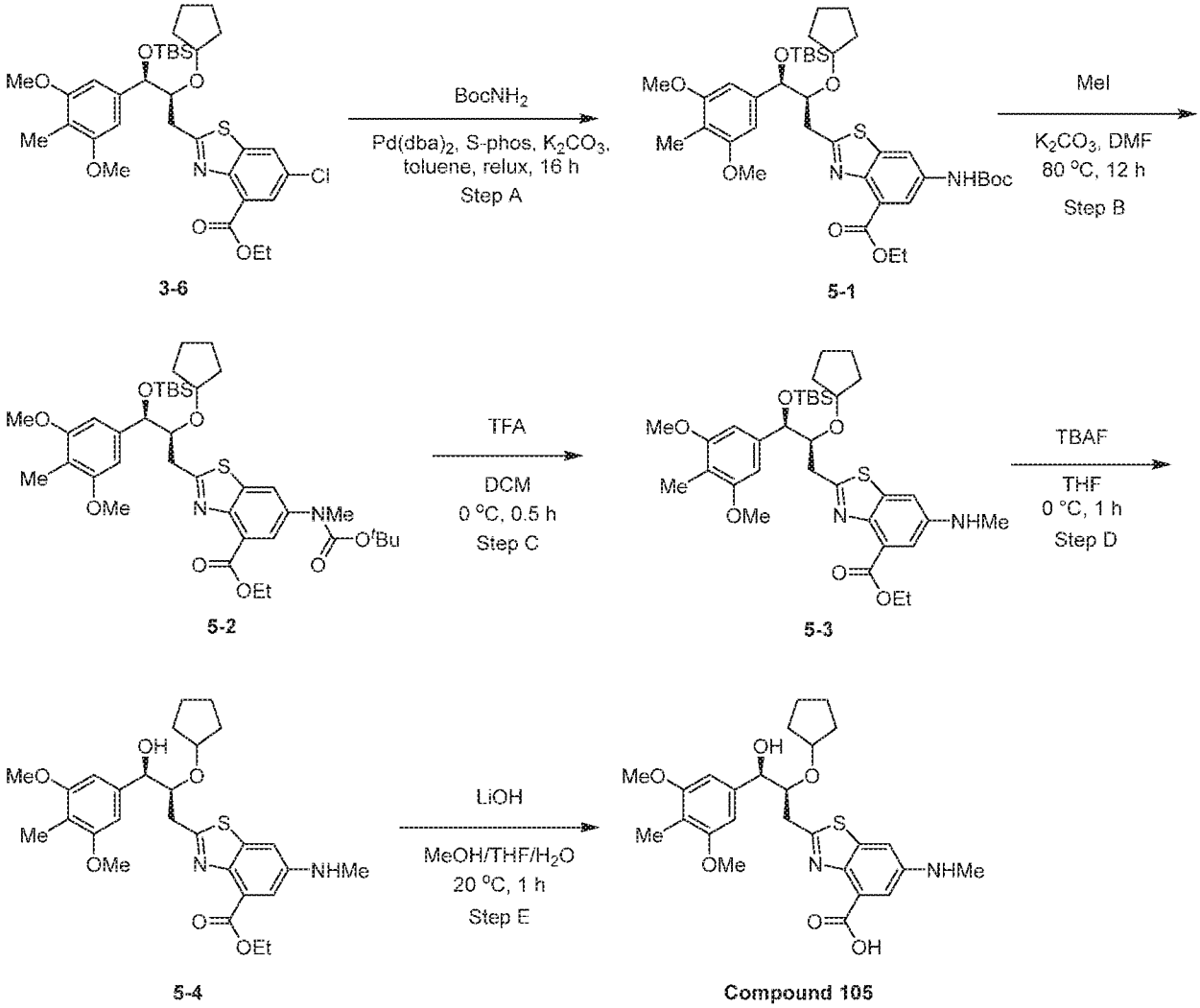
[0257] Dimethyl 3,3'-disulfanediylbis(2-amino-5-(methoxymethyl)benzoate) (**4-7**) was synthesized according to the procedures described for the preparation of **Example A1** (step **B** to step **D** in Scheme **1**) by using methyl 2-amino-5-(methoxymethyl)benzoate in step **B**. LC-MS: m/z 474.8 $(M+Na)^+$.



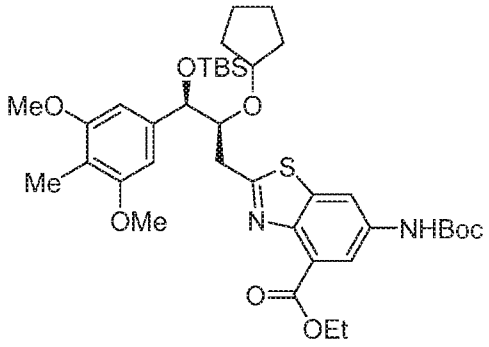
[0258] 2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(methoxymethyl)benzo[d]thiazole-4-carboxylic acid **(Compound 104)** was synthesized according to the procedures described for the preparation of **Example A1** (step **Q** to step **S** in Scheme **1**) by using dimethyl 3,3'-disulfanediylbis(2-amino-5-(methoxymethyl)benzoate) (**4-7**) and (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3,5-dimethoxy-4-methylphenyl)butanoic acid (**3-5**) in step Q. LC-MS: m/z 516.1 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 1.2 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 6.67 (s, 2H), 4.69 (d, J = 5.6 Hz, 1H), 4.65 (s, 2H), 4.04 - 3.99 (m, 1H), 3.97 - 3.90 (m, 1H), 3.83 (s, 6H), 3.53 - 3.48 (m, 2H), 3.46 (s, 3H), 1.99 (s, 3H), 1.55 - 1.34 (m, 8H).

Example A5

2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(methylamino)benzo[d]thiazole-4-carboxylic acid (Compound 105)

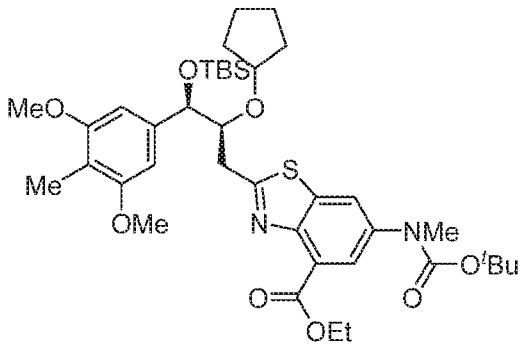


[0259] Step A: Ethyl 6-((tert-butoxycarbonyl)amino)-2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)benzo[d]thiazole-4-carboxylate



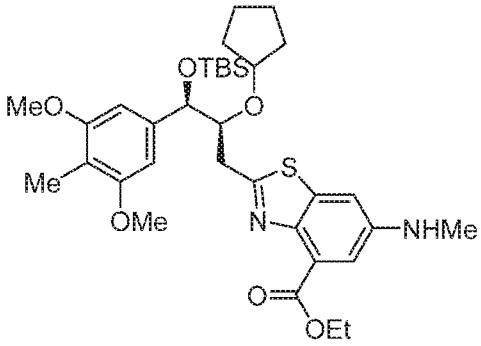
[0260] To a solution of ethyl 2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-6-chloro-1,3-benzothiazole-4-carboxylate (500 mg, 771.22 μmol) and tert-butyl carbamate (271.04 mg, 2.31 mmol) in toluene (10 mL) was added $Pd(dba)_2$ (44.35 mg, 77.12 μmol), K_2CO_3 (319.76 mg, 2.31 mmol) and *S*-Phos (63.32 mg, 154.24 μmol). The mixture was stirred at 100 °C for 16 h. The reaction mixture was quenched by addition of H_2O (10 mL) at 0 °C, extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (PE/EtOAc = 100/1 to 10/1) to afford ethyl 6- (tert-butoxycarbonylamino) -2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-1,3-benzothiazole-4-carboxylate (500 mg, 88.9% yield). ^1H NMR (400MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.66 (d, J = 2.1 Hz, 1H), 6.70 (s, 1H), 6.56 (s, 2H), 4.73 (d, J = 4.6 Hz, 1H), 4.48 - 4.42 (m, 3H), 3.95 - 3.90 (m, 1H), 3.82 (s, 6H), 3.45 - 3.40 (m, 1H), 3.31 - 3.25 (m, 1H), 2.06 (s, 3H), 1.53 (s, 9H), 1.43 - 1.25 (m, 10H), 1.43 - 1.24 (m, 1H), 0.91 (s, 9H), 0.07 (s, 3H), -0.12 (s, 3H).

[0261] Step B Ethyl 6-((tert-butoxycarbonyl)(methyl)amino)-2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)benzo[d]thiazole-4-carboxylate



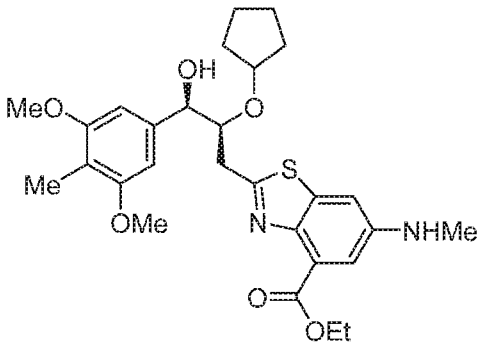
[0262] To a solution of ethyl 6- (tert-butoxycarbonylamino) -2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-1,3-benzothiazole-4-carboxylate (200 mg, 274.35 μmol) in DMF (2 mL) was added K_2CO_3 (189.58 mg, 1.37 mmol) and MeI (194.70 mg, 85.40 μL). The mixture was stirred at 80 °C for 12 h. After cooling, the reaction mixture was diluted with H_2O (5 mL), extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*. TLC (SiO_2, PE/EtOAc = 10/1) to afford ethyl 6-[tert-butoxycarbonyl (methyl) amino]-2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-1,3-benzothiazole-4-carboxylate (40 mg, 19.6% yield). LC-MS: m/z 765.3 $(M+Na)^+$.

[0263] Step C: Ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-6-(methylamino)benzo[d]thiazole-4-carboxylate



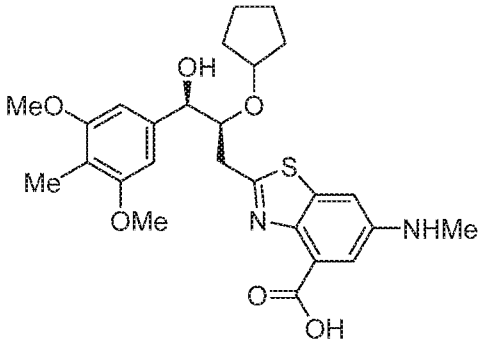
[0264] To a solution of ethyl 6-[tert-butoxycarbonyl (methyl) amino]-2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-1,3-benzothiazole-4-carboxylate (30 mg, 40.37 μmol) in DCM (1 mL) was added TFA (29.89 μL, 400 μmol). The reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford ethyl 2- ((2S,3R) -3- ((tert-butyldimethylsilyl) oxy) -2- (cyclopentyloxy) -3- (3,5-dimethoxy-4-methylphenyl) propyl) -6- (methylamino) benzo[d]thiazole-4-carboxylate (22.5 mg, 86.7% yield), which was used for next step without further purification. LC-MS: m/z 643.1 $(M+H)^+$.

[0265] Step D: Ethyl 2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(methylamino)benzo[d]thiazole-4-carboxylate



[0266] To a solution of ethyl 2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-6- (methylamino) -1,3-benzothiazole-4-carboxylate (30 mg, 46.66 μmol) in THF (0.5 mL) was added TBAF (466.62 μL, 466.62 μmol, 1 M solution in THF) at 0 °C. The mixture was stirred at 0 °C for 1 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 (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford ethyl 2-[(2S,3R) -2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) -3-hydroxy-propyl]-6- (methylamino) -1,3-benzothiazole-4-carboxylate (20 mg, 81.1% yield), which used for next step without further purification. LC-MS: m/z 528.7 $(M+H)^+$.

[0267] Step E: 2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(methylamino)benzo[d]thiazole-4-carboxylic acid (Compound 105)

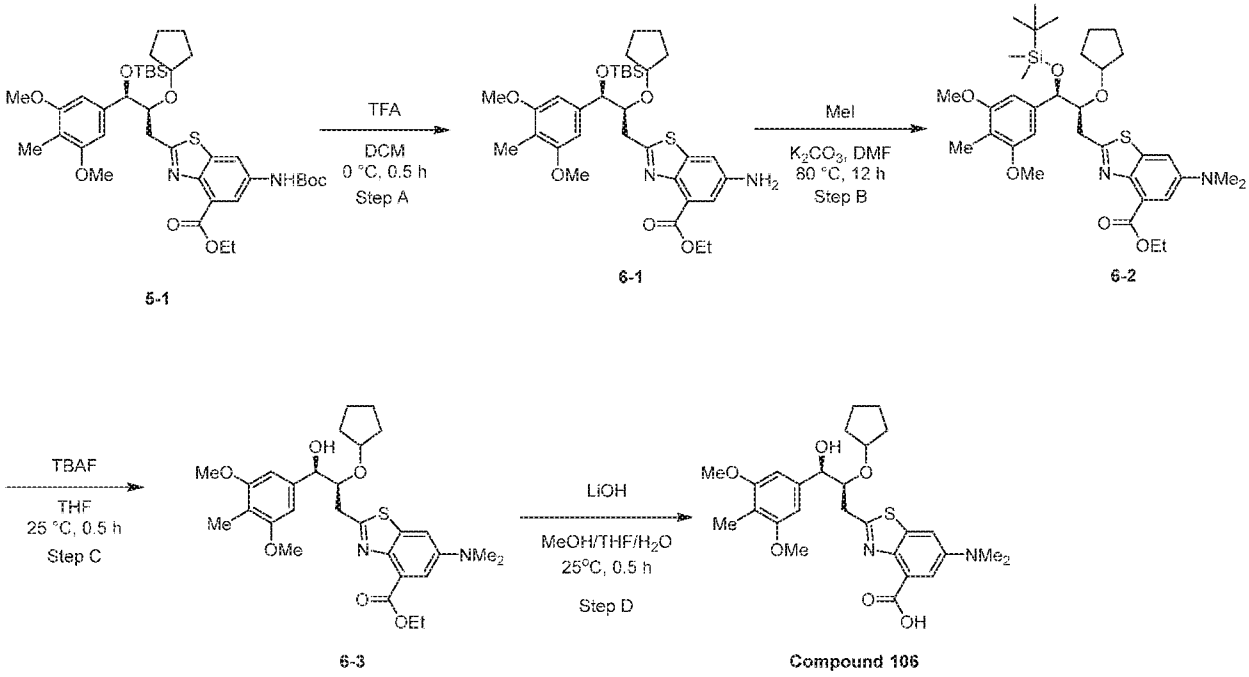


[0268] To a solution of ethyl 2-[(2S,3R) -2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) -3-hydroxy-propyl]-6- (methylamino) -1,3-benzothiazole-4-carboxylate (20 mg, 37.83 μmol) in THF (0.8 mL), MeOH (0.2 mL) and H_2O (0.2 mL) was added LiOH (4.53 mg, 189.16 μmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*. HPLC (Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 50% B to 90% B in 10 min) to give 2-[(2S,3R) -2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) -3-hydroxy-propyl]-6-(methylamino)-1,3-benzothiazole-4-carboxylic acid (7.92 mg, 41.8% yield). LC-MS: m/z 501.3 $(M+H)^+$.

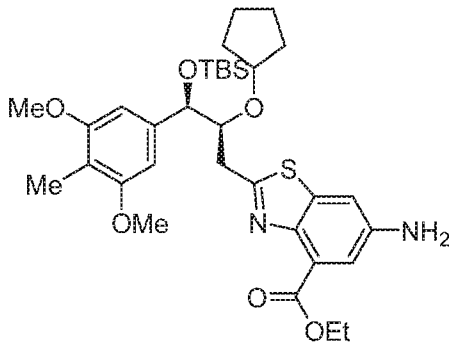
^{1}H NMR (400MHz, $CDCl_3$) δ 7.57 (d, J = 2.3 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 6.57 (s, 2H), 4.93 (d, J = 4.3 Hz, 1H), 4.02 - 3.97 (m, 2H), 3.84 (s, 6H), 3.31 - 3.24 (m, 1H), 3.11 (dd, J = 3.5, 15.2 Hz, 1H), 2.92 (s, 3H), 2.06 (s, 3H), 1.61 - 1.40 (m, 8H).

Example A6

2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(dimethylamino)benzo[d]thiazole-4-carboxylic acid (Compound 106)



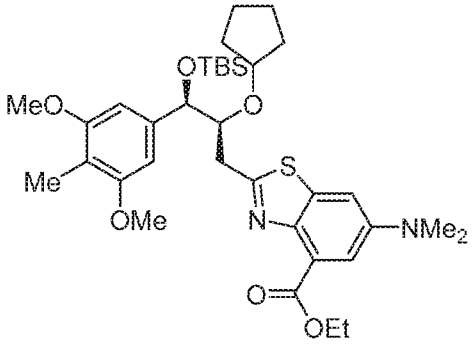
[0269] Step A: ethyl 6-amino-2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)benzo[d]thiazole-4-carboxylate



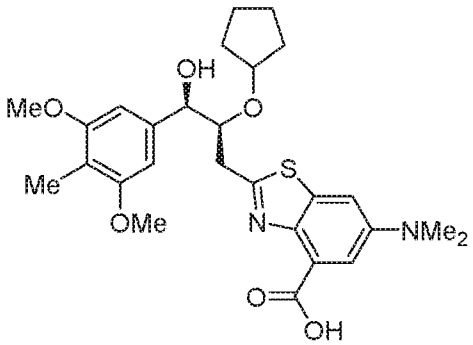
[0270] To a solution of ethyl 6- (tert-butoxycarbonylamino) -2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-1,3-benzothiazole-4-carboxylate (100 mg, 137.17 μmol) in DCM (1 mL) was added TFA (101.56 μL, 1.37 mmol). The reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched by addition H_2O (10

mL), extracted with DCM (10 mL x 3). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford ethyl 6-amino-2-[(2S,3R) -3-[tert-butyl (dimethyl) silyl]oxy-2- (cyclopentoxy) -3- (3,5-dimethoxy-4-methyl-phenyl) propyl]-1,3-benzothiazole-4-carboxylate (80 mg, 92.74% yield), which used for next step without further purification. LC-MS: m/z 629.2 $(M+H)^+$.

[0271] Step B: ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-6-(dimethylamino)benzo[d]thiazole-4-carboxylate



[0272] To a solution of ethyl 6-amino-2- ((2S,3R) -3- ((tert-butyldimethylsilyl) oxy) -2- (cyclopentyloxy) -3- (3,5-dimethoxy-4-methylphenyl) propyl) benzo[d]thiazole-4-carboxylate (60 mg, 95.41 μmol) in DMF (1 mL) was added K_2CO_3 (39.56 mg, 286.22 μmol) and MeI (23.76 μL, 381.62 μmol). The reaction mixture was stirred at 80 °C for 12 h. After cooling, the reaction mixture was diluted with H_2O (10 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, filtered, and concentrated to afford ethyl 2- ((2S,3R) -3- ((tert-butyldimethylsilyl) oxy) -2- (cyclopentyloxy) -3- (3,5-dimethoxy-4-methylphenyl) propyl) -6- (dimethylamino) benzo[d]thiazole-4-carboxylate (55 mg, 87.75% yield), which used for next step without further purification. LC-MS: m/z 657.3 $(M+H)^+$.

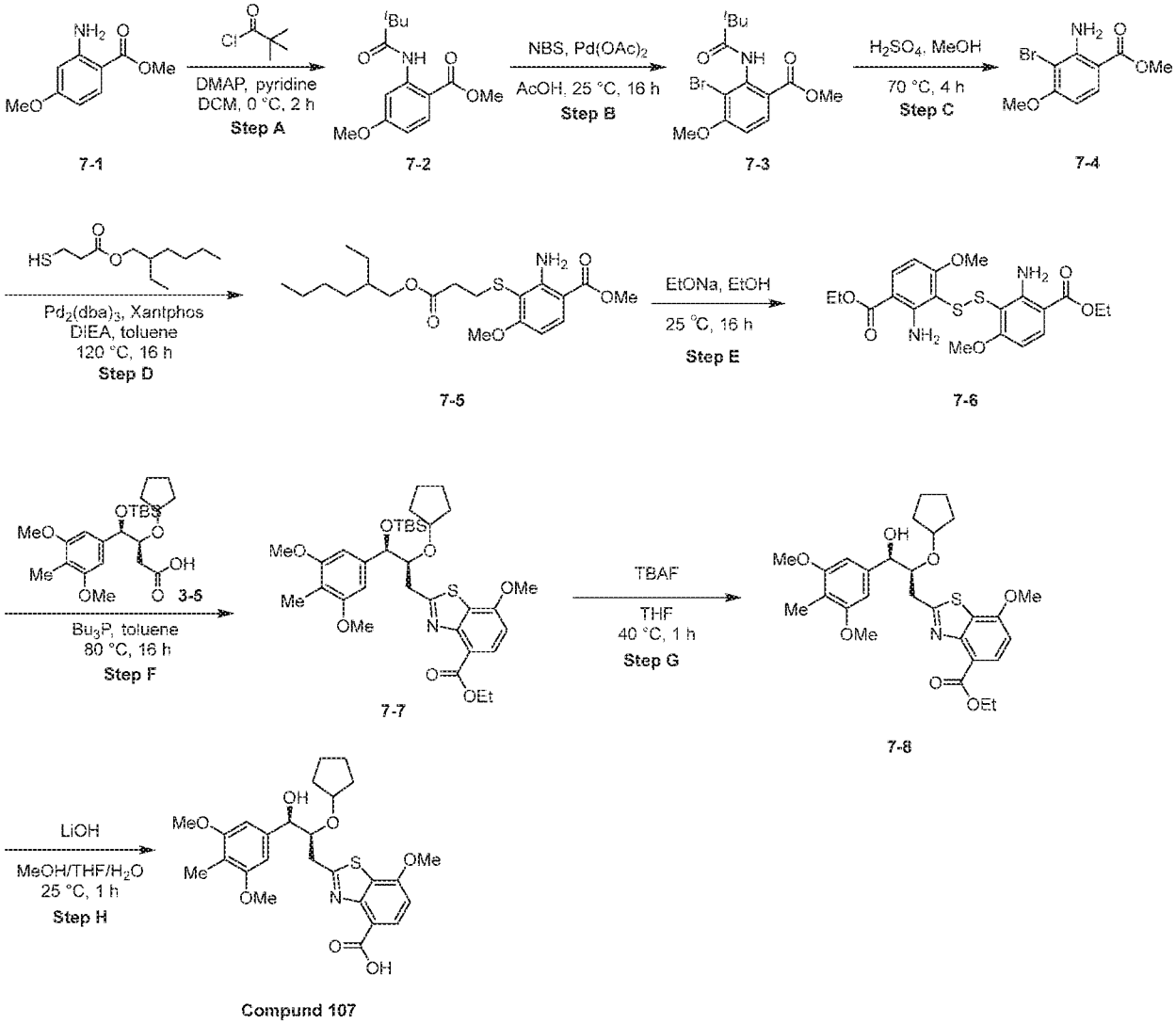


[0273] 2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-6-(dimethylamino)benzo[d]thiazole-4-carboxylic acid **Example A6 (Compound 106)** was synthesized

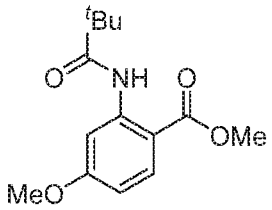
according to the procedures described for the preparation of **Example A5** (step **D** to step **E** in Scheme **5**) by using ethyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-6-(dimethylamino)benzo[d]thiazole-4-carboxylate (**6-2**) in step **D**. LC-MS: m/z 515.3 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 7.73 (d, J = 2.7 Hz, 1H), 7.19 (d, J = 2.6 Hz, 1H), 6.58 (s, 2H), 4.94 (d, J = 4.3 Hz, 1H), 4.03 - 3.97 (m, 2H), 3.85 (s, 6H), 3.31 - 3.24 (m, 1H), 3.14 - 3.09 (m, 1H), 3.08 (s, 6H), 2.07 (s, 3H), 1.56 - 1.32 (m, 8H).

Example A7

2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-7-methoxybenzo[d]thiazole-4-carboxylic acid (Compound 107)

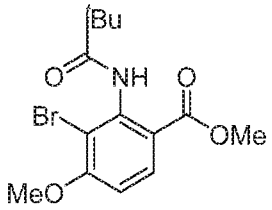


[0274] Step A: methyl 4-methoxy-2-pivalamidobenzoate



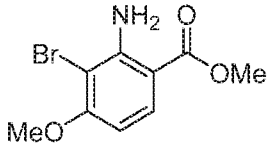
[0275] To a solution of methyl 2-amino-4-methoxybenzoate (25 g, 137.98 mmol) in DCM (200 mL) was added pyridine (22.27 mL, 275.96 mmol) and DMAP (168.57 mg, 1.38 mmol) at 25 °C. Then 2,2-dimethylpropanoyl chloride (18.67 mL, 151.78 mmol) was added to the mixture in dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with 1N HCl solution (50 mL) and diluted with DCM (100 mL). The organic layer was separated, washed with 1N HCl solution (40 mL), *sat. aq.* $NaHCO_3$ (50 mL) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude methyl 4-methoxy-2-pivalamidobenzoate (18 g, 60.9% yield), which used for the next step directly without further purification. LC-MS: m/z 266.3$(M+H)^+$.

[0276] Step B: methyl 3-bromo-4-methoxy-2-pivalamidobenzoate

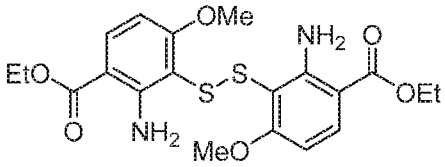


[0277] To a solution of methyl 2-(2,2-dimethylpropanoylamino)-4-methoxy-benzoate (36 g, 135.69 mmol) in toluene (400 mL) was added $Pd(OAc)_2$ (6.09 g, 27.14 mmol), NBS (53.13 g, 298.53 mmol) and 4-methylbenzenesulfonic acid (46.73 g, 271.39 mmol). The reaction mixture was stirred at 25 °C for 16 h. Then the reaction mixture was diluted with H_2O (200 mL) and filtered. The filtrate was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~15% EtOAc/PE gradient @ 65 mL/min) to give methyl 3-bromo-2-(2,2-dimethylpropanoylamino)-4-methoxy-benzoate (4.8 g, 10.3% yield). LC-MS: m/z 344.2 $(M+H)^+$.

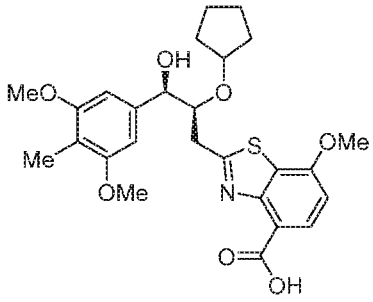
[0278] Step C: methyl 2-amino-3-bromo-4-methoxybenzoate



[0279] To a solution of methyl 3-bromo-4-methoxy-2-pivalamidobenzoate (4.8 g, 13.95 mmol) in MeOH (2 mL) was added *conc*. H_2SO_4 (44.66 g, 24.27 mL) dropwise at 0 °C. The reaction mixture was degassed and purged with N_2 for 3 times. The resulting mixture was stirred at 70 °C for 4 h under N_2 atmosphere. After cooling, the reaction was diluted with water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with PE (10 mL) and the suspension isolated via filtration. The filter cake was washed with PE (20 mL) and then dried under reduced pressure to give methyl 2-amino-3-bromo-4-methoxybenzoate (2.4 g, 66.2% yield), which used for the next step directly without further purification. LC-MS: m/z 262.1 $(M+H)^+$. ^1H NMR (400MHz, DMSO-*d6*) δ 7.82 (d, *J* = 9.0 Hz, 1H), 6.45 (d, *J* = 9.0 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H).



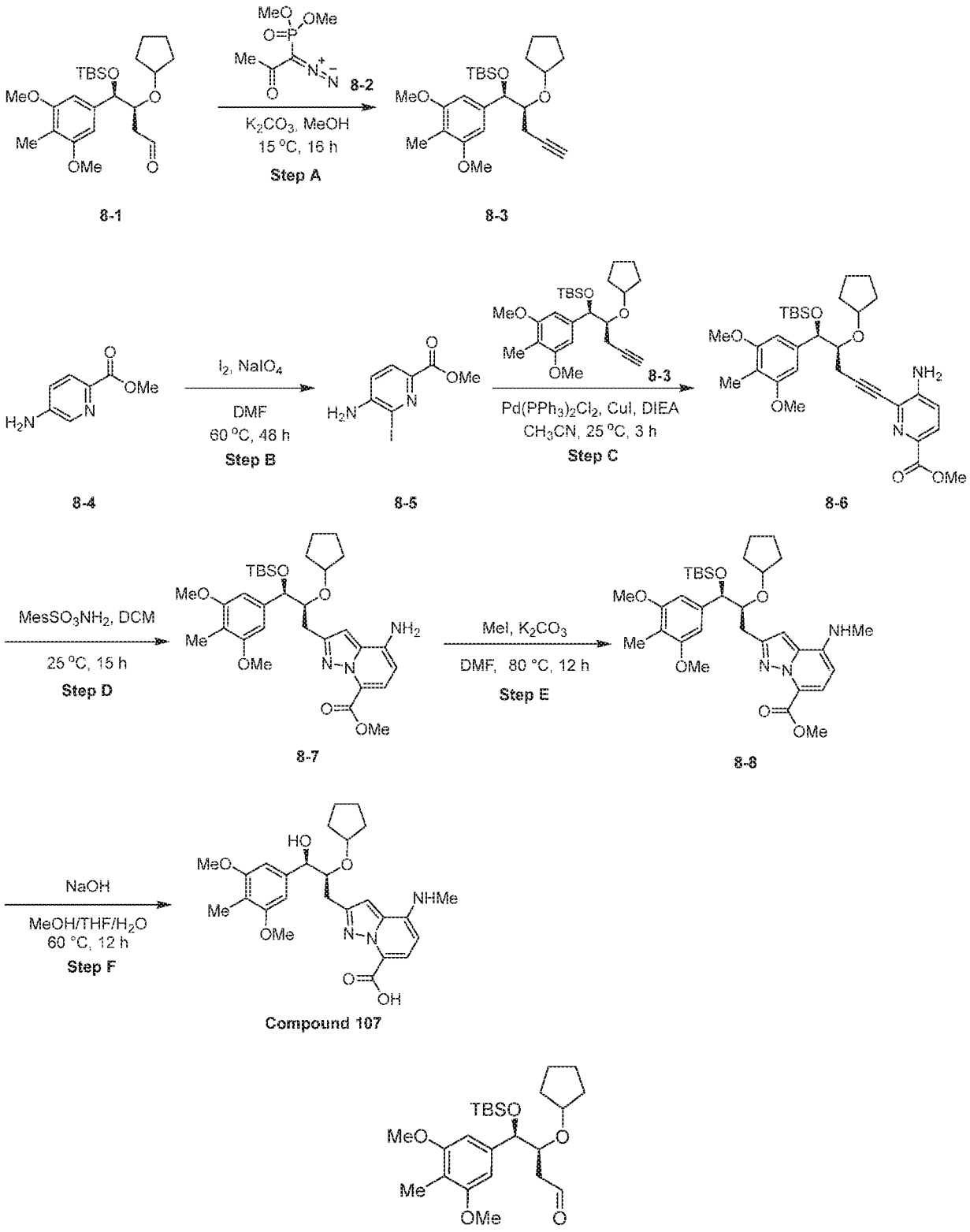
[0280] Diethyl 3,3'-disulfanediylbis(2-amino-4-methoxybenzoate) (**7-6**) was synthesized according to the procedures described for the preparation of **Example A1** (step **C** to step **D** in Scheme **1**) by using methyl 2-amino-3-bromo-4-methoxybenzoate (**7-4**) in step **C**. LC-MS: m/z 474.9 $(M+Na)^+$.



[0281] 2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-7-methoxybenzo[d]thiazole-4-carboxylic acid **(Compound 107)** was synthesized according to the procedures described for the preparation of **Example A1** (step **Q**, **S** and **R** in Scheme **1**) by using diethyl 3,3'-disulfanediylbis(2-amino-4-methoxybenzoate) (**7-6**) in step **D**. LC-MS: m/z 502.3 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) *δ* 13.36 (br s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 2H), 4.95 (d, *J* = 4.3 Hz, 1H), 4.07 (s, 3H), 4.06 - 3.98 (m, 2H), 3.85 (s, 6H), 3.39 (dd, *J* = 8.3, 15.1 Hz, 1H), 3.21 (dd, *J* = 3.7, 15.1 Hz, 1H), 2.06 (s, 3H), 1.59 - 1.34 (m, 8H).

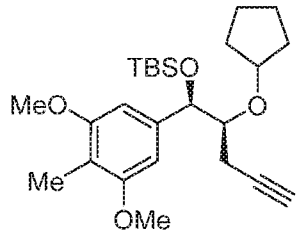
Example A8

2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-4-(methylamino)pyrazolo[1,5-a]pyridine-7-carboxylic acid (Compound 108)



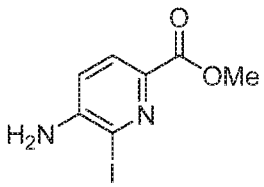
[0282] (3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(cyclopentyloxy)-4-(3,5-dimethoxy-4-methylphenyl)butanal (**8-1**) was synthesized according to the procedures described for the preparation of **Example A1** (step **H** to step **O** in Scheme **1**) by using 3,5-dimethoxy-4-methylbenzene-1-carbaldehyde in step **H**.

[0283] Step A: tert-butyl(((1R,2S)-2-(cyclopentyloxy)-1-(3,5-dimethoxy-4-methylphenyl)pent-4-yn-1-yl)oxy)dimethylsilane



[0284] At 0 °C, 1-diazo-1-dimethoxyphosphoryl-propan-2-one (3.8 g, 19.8 mmol) was added drop wisely to the mixture of (3S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-(cyclopentoxy)-4-(3,5-dimethoxy-4-methyl-phenyl)butanal (7.2 g, 16.5 mmol) and K_2CO_3 (4.56 g, 33.0 mmol) in MeOH (70 mL). The reaction mixture was stirred at 15 °C for 16 h under nitrogen. The mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 220g SepaFlash® Silica Flash Column, Eluent of 0~4% EtOAc/PE gradient @ 150 mL/min) to give tert-butyl-[(1R,2S)-2-(cyclopentoxy)-1-(3,5-dimethoxy-4-methyl-phenyl)pent-4-ynoxy]-dimethyl-silane (3.2 g, 44.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 2H), 4.59 - 4.58 (m, 1H), 3.85 -3.81 (m, 7H), 3.50 - 3.46 (m, 1H), 2.48 - 2.46 (m, 2H), 2.07 (s, 3H), 1.97 (s, 1H), 1.46 - 1.34 (m, 8H), 0.90 (s, 9H), 0.07 (s, 3H), -0.15 (s, 3H).

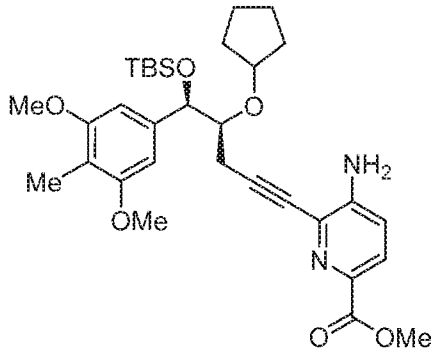
[0285] Step B: methyl 5-amino-6-iodopicolinate



[0286] To a solution of methyl 5-aminopicolinate (10 g, 65.7 mmol) in DMF (80 mL) was added $NaIO_4$ (5.61 g, 26.2 mmol) and I_2 (13.4 g, 52.7 mmol). The reaction mixture was stirred at 60 °C for 48 h. After cooling, to the reaction mixture was added 10% *aq.* sodium sulfite solution (100 mL). The resulting mixture was stirred for 10 minutes. The crystals were collected by filtration. The collected crystals were washed with water, dried under reduced pressure to give the methyl 5-amino-6-iodo-pyridine-2-

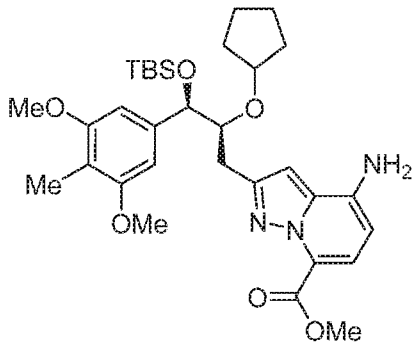
carboxylate (7.84 g, 42.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 4.68 (brs, 2H), 3.93 (s, 3H).

[0287] Step C: methyl 5-amino-6-((4S,5R)-5-((tert-butyldimethylsilyl)oxy)-4-(cyclopentyloxy)-5-(3,5-dimethoxy-4-methylphenyl)pent-1-yn-1-yl)picolinate



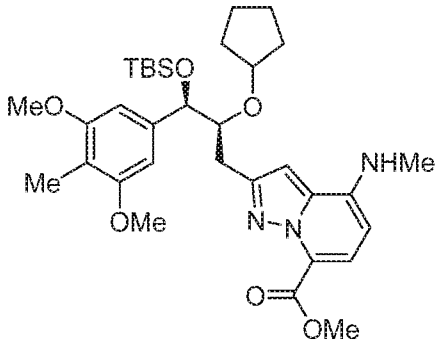
[0288] To a solution of tert-butyl-[(1R,2S)-2-(cyclopentoxy)-1-(3,5-dimethoxy-4-methyl-phenyl)pent-4-ynoxy]-dimethyl-silane (1.71 g, 3.96 mmol) and methyl 5-amino-6-iodo-pyridine-2-carboxylate (1 g, 3.60 mmol) in MeCN (40 mL) was added $Pd(PPh_3)_2Cl_2$ (252 mg, 360 μmol), CuI (68.5 mg, 360 μmol) and DIEA (3.13 mL, 17.95 mmol). The resulting mixture was stirred at 25 °C for 3 h. The mixture was diluted with water (200 mL), extracted with EtOAc (150 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/PE gradient @ 100 mL/min) to give methyl 5-amino-6-[(4S,5R)-5-[tert-butyl(dimethyl)silyl]oxy-4-(cyclopentoxy)-5-(3,5-dimethoxy-4-methyl-phenyl)pent-1-ynyl]pyridine-2-carboxylate (1.77 g, 84.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.55 (s, 2H), 4.75 (s, 2H), 4.65 (d, J = 6.0 Hz, 1H), 3.93 (s, 3H), 3.87 (d, J = 2.8 Hz, 1H), 3.83 (s, 6H), 3.66 - 3.57 (m, 1H), 2.91 - 2.81 (m, 1H), 2.80 - 2.70 (m, 1H), 2.08 (s, 3H), 1.73 - 1.63 (m, 2H), 1.52 - 1.30 (m, 6H), 0.91 (s, 9H), 0.08 (s, 3H), -0.13 (s, 3H).

[0289] Step D: methyl 4-amino-2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)pyrazolo[1,5-a]pyridine-7-carboxylate



[0290] The mixture of tert-butyl ((mesitylsulfonyl)oxy)carbamate (946 mg, 3 mmol) and TFA (5 mL) was stirred at 0 °C for 1 h. The mixture was poured into ice-cold water (150 mL), extracted with DCM (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the filtrate was added dropwise to a solution of methyl 5-amino-6-[(4S,5R)-5-[tert-butyl(dimethyl)silyl]oxy-4-(cyclopentoxy)-5-(3,5-dimethoxy-4-methyl-phenyl)pent-1-ynyl]pyridine-2-carboxylate (0.96 g, 1.65 mmol) in DCM (20 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 15 h. The reaction mixture was quenched with *sat. aq.* $NaHCO_3$ (150 mL). The organic layer was separated, dried over anhydrous 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 0~20~40% EtOAc/PE gradient @ 80 mL/min) to give methyl 4-amino-2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3,5-dimethoxy-4-methyl-phenyl)propyl]pyrazolo[1,5-a]pyridine-7-carboxylate (168 mg, 17.1% yield). LC-MS: m/z 598.8 $(M+H)^+$.

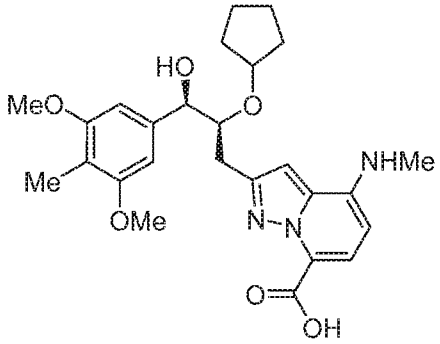
[0291] Step E: methyl 2-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)propyl)-4-(methylamino)pyrazolo[1,5-a]pyridine-7-carboxylate



[0292] To a solution of methyl 4-amino-2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3,5-dimethoxy-4-methyl-phenyl)propyl]pyrazolo[1,5-a]pyridine-7-carboxylate (84 mg, 141 μmol) in DMF (2 mL) was added K_2CO_3 (58.3 mg, 422 μmol) and MeI (70.0 μL, 1.12 mmol). The reaction mixture was stirred at 80 °C for 12 h. After cooling, the mixture was diluted with water (30 mL), extracted with EtOAc (30 mL x 4). The combined organic layers were dried over anhydrous Na_2SO_4,

filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/PE gradient @ 100 mL/min) to give methyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3,5-dimethoxy-4-methyl-phenyl)propyl]-4-(methylamino)pyrazolo[1,5-a]pyridine-7-carboxylate (20 mg, 23.3% yield). LC-MS: m/z 634.0 $(M+Na)^+$.

[0293] Step F: 2-((2S,3R)-2-(cyclopentyloxy)-3-(3,5-dimethoxy-4-methylphenyl)-3-hydroxypropyl)-4-(methylamino)pyrazolo[1,5-a]pyridine-7-carboxylic acid



[0294] To a solution of methyl 2-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-(cyclopentoxy)-3-(3,5-dimethoxy-4-methyl-phenyl)propyl]-4-(methylamino)pyrazolo[1,5-a]pyridine-7-carboxylate (20 mg, 32.7 μmol) in THF (2 mL), MeOH (5 mL) and H_2O (2 mL) was added NaOH (261 mg, 6.54 mmol). The reaction mixture was stirred at 60 °C for 12 h. The solvent was removed under vacuum. The residue was diluted with water (5 mL), acidified with 6N HCl to *p*H = 4-5. The mixture was extracted with EtOAc (30 mL x 3). The organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to give a residue. The residue was purified by *prep*. HPLC (Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 50% B to 80% B in 8 min) to give 2-[(2S,3R)-2-(cyclopentoxy)-3-(3,5-dimethoxy-4-methyl-phenyl)-3-hydroxy-propyl]-4-(methylamino)pyrazolo[1,5-a]pyridine-7-carboxylic acid (2.33 mg, 14.52% yield). LC-MS: m/z 484.3 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 8.2 Hz, 1H), 6.71 (s, 1H), 6.64 (s, 2H), 6.24 (d, J = 8.2 Hz, 1H), 4.61 - 4.58 (m, 2H), 3.87 - 3.74 (m, 8H), 3.22 - 3.14 (m, 1H), 3.07 - 3.01 (m, 1H), 3.00 (s, 3H), 1.99 (s, 3H), 1.46 -1.24 (m, 8H).

[0295] The compounds in Table 1 can be or were synthesized using a similar procedure described in the Examples above using the appropriate starting materials. Data for certain compounds is shown in the Table below. Purification conditions for certain compounds is as follows.

[0296] Prep. HPLC separation conditions for compound 102: Column: Welch Xtimate C18 150*30 mm*5 μm; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 57% B to 87% B in 7 min.

[0297] Prep. HPLC separation conditions for compound 103: Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 50% B to 80% B in 10 min.

[0298] Prep. HPLC separation conditions for compound 104: Column: Welch Xtimate C18 150*30 mm*5 μm; Mobile Phase A: Water (0.01% NH_3H_2O + 10 mM NH_4HCO_3), Mobile Phase B: CH_3CN; Gradient: 20% B to 50% B in 9 min.

[0299] Prep. HPLC separation conditions for compound 106: Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 50% B to 90% B in 10 min.

[0300] Prep. HPLC separation conditions for compound 107: Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 50% B to 85% B in 10 min.

[0301] Prep. HPLC separation conditions for compound 109: Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% CF3COOH), Mobile Phase B: CH_3CN; Gradient: 50% B to 90% B in 10 min.

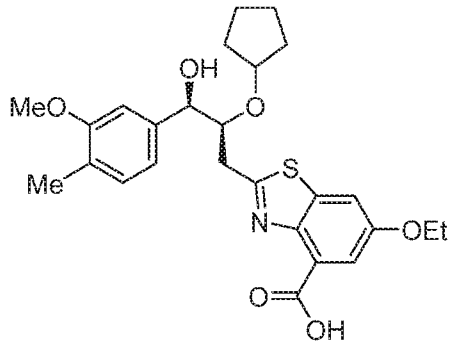
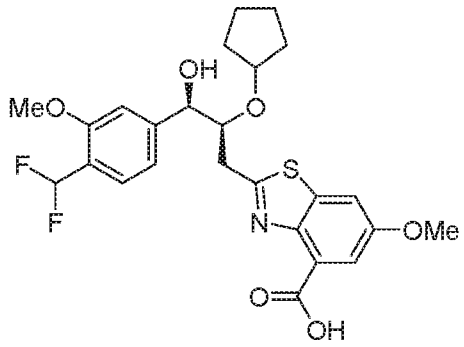
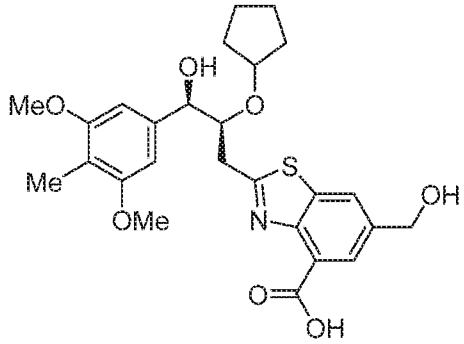
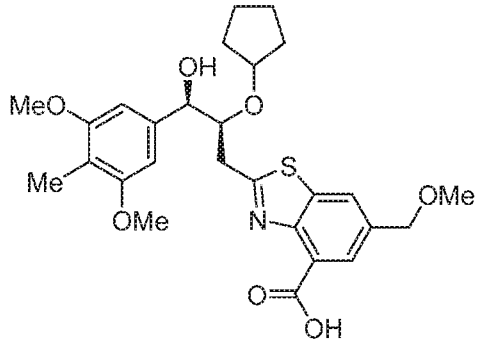
[0302] Prep. HPLC separation conditions for compound 110: Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 55% B to 95% B in 9 min.

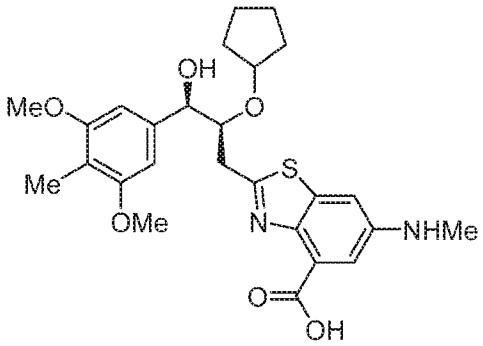
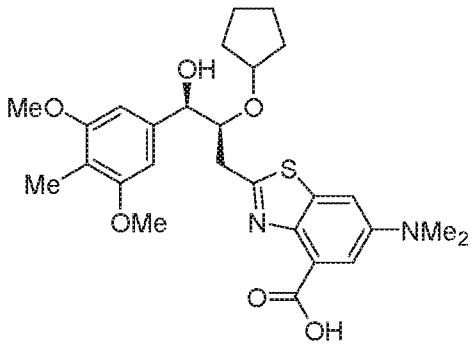
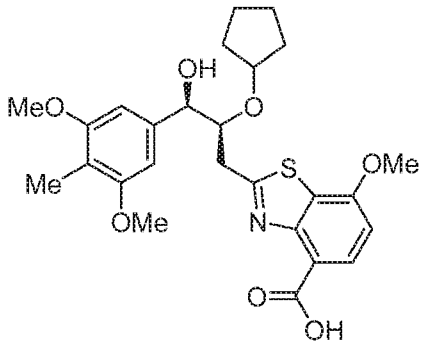
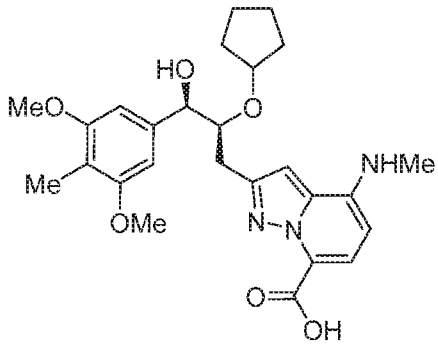
[0303] Prep. HPLC separation conditions for compound 111: Column: Boston Green ODS (150*30 mm*5 μm); Mobile Phase A: Water (0.225% HCOOH), Mobile Phase B: CH_3CN; Gradient: 60% B to 90% B in 8 min.

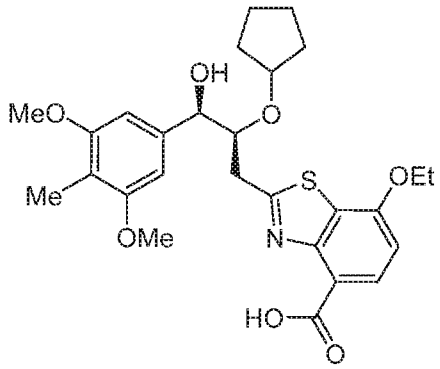
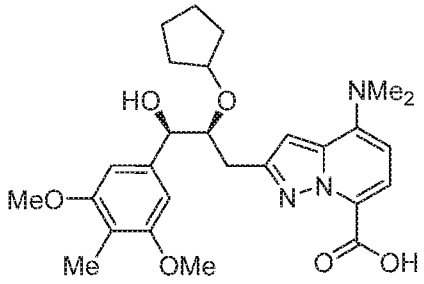
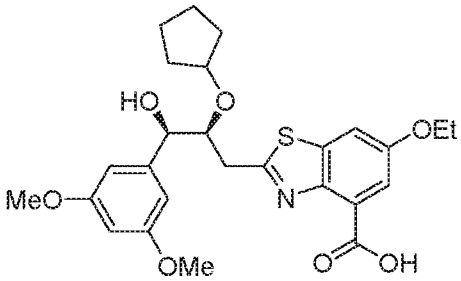
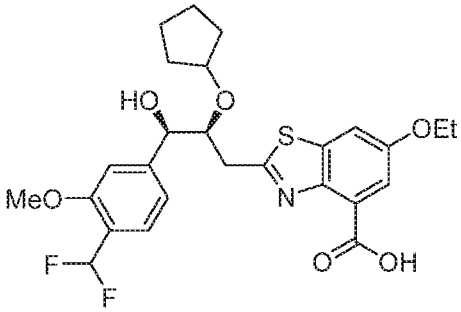
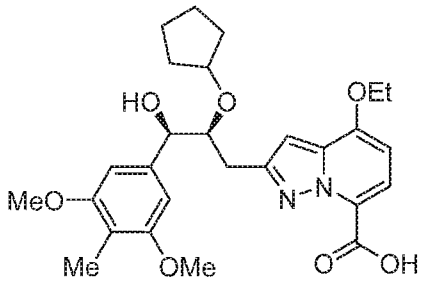
[0304] Prep. HPLC separation conditions for compound 112: Column: Phenomenex Gemini-NX C18 75*30 mm*3 μm; Mobile Phase A: Water (0.225% HCOOH), Mobile Phase B: CH_3CN; Gradient: 63% B to 93% B in 8 min.

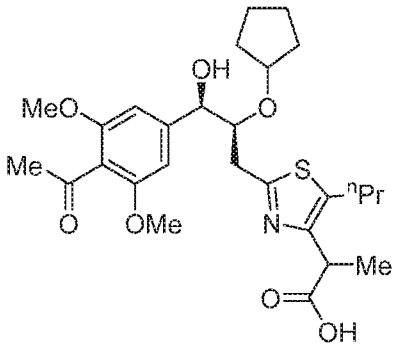
[0305] Prep. HPLC separation conditions for compound 113: Column: Kromasil 100-5-C18; Mobile Phase A: Water (0.1% HCOOH), Mobile Phase B: CH_3CN; Gradient: 55% B to 100% B in 10 min.

[0306] Prep. HPLC separation conditions for compound 114: Column: DAICEL CHIRALPAK IF (250 mm*30 mm*10 μm); Mobile Phase A: Water (0.1%NH_3H_2O), Mobile Phase B: EtOH; Gradient: 20% B to 20% B in 8 min.

Compound	Structure	LC-MS: m/z
101		486.1 $(M+H)^+$
102		508.0 $(M+H)^+$
103		502.3 $(M+H)^+$
104		538.1 $(M+Na)^+$

Compound	Structure	LC-MS: m/z
105		501.3 $(M+H)^+$
106		515.3 $(M+H)^+$
107		502.3 $(M+H)^+$
108		484.3 $(M+H)^+$

Compound	Structure	LC-MS: m/z
109		516.4 $(M+H)^+$
110		498.4 $(M+H)^+$
111		502.1 $(M+H)^+$
112		522.0 $(M+H)^+$
113		499.4 $(M+H)^+$

Compound	Structure	LC-MS: m/z
114		520.0 $(M+H)^+$

Biological Assays

In Vitro LPA1 functional antagonist Assay

[0307] CHO-K1 cells overexpressing human LPA1 are 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 are 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 is prepared fresh. Cells are loaded with dye prior to testing. Media is aspirated from cells and replaced with 20 µL Dye Loading Buffer. Cells are incubated for 30-60 minutes at 37°C. After dye loading, cells are removed from the incubator and 10 µL 3X test compound is added. Cells are incubated for 30 minutes at room temperature in the dark to equilibrate plate temperature followed by Oleoyl LPA challenge at the 0.018 µM. Compound antagonist activity is measured on a FLIPR Tetra (MDS). Calcium mobilization is monitored for 2 minutes and 10 µL Oleoyl LPA in HBSS / 20 mM Hepes is added to the cells 5 seconds into the assay. Compound activity is 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)).

In vitro LPA1 Calcium flux antagonist assay

[0308] 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 (MDS). 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.

[0309] 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)).

[0310] **Table B1** shows the biological activity of compounds in *in vitro* LPA1 Calcium flux antagonist assay. Activity of the tested compounds is provided in Table B1 below as follows: +++ = IC_{50} < 10 nM; ++ = IC_{50} 10 nM – 100 nM; + = IC_{50} > 100 nM.

Table B1

Compound	Activity
101	+++
102	+++
103	++
104	+++
105	+++

Compound	Activity
106	+++
107	+++
108	++
109	+++
110	+

Compound	Activity
111	++
112	++
113	++
114	++

***In Vivo* Studies**

Pharmacokinetics Measurements in Mice

[0311] The PK properties of selected compounds were measured in CD1 female mice following single oral (5 mg/kg) administration.

[0312] Compounds 103 and 104 were prepared in a 1 mg/mL solution of 10% Solutol HS15 and 90% saline for oral administrations at 5 mL/kg, respectively, and administered to 3 mice/3 groups. After dosing, blood collection was performed by dorsal metatarsal vein sampling at 0.25, 0.5, 1, 2, 4, 6, 8, 24 h, followed by centrifugation to obtain plasma. Samples were stored frozen at -80 °C prior to compound extraction and LC-MS/MS analysis. Pharmacokinetic parameters of compounds 103 and 104 in mice were calculated by standard noncompartmental modeling from the systemic plasma concentration-time profile.

[0313] Table B2 shows the mean pharmacokinetic parameters of compounds 103 and 104 in mice (CD1; female) determined by the non-compartmental model.

Table B2

PK parameter	Compound	
	103	**104**
T_{max} (h)	0.500	0.250
C_{max} (ng/mL)	463	3837
AUC_{last} (h*ng/mL)	1643	6947

Pharmacokinetics Measurements in Rats

[0314] The PK properties of selected compounds were measured in SD Male rats following single oral (5 mg/kg) and Intravenous Administration (1 mg/kg).

[0315] Compounds 103 and 104 were prepared in a 1 mg/mL solution of 10% Solutol HS15 and 90% saline for oral administrations at 5 mL/kg and 0.2 mg/mL solution of 10% Solutol HS15 and 90% saline for intravenous administrations at 1 mL/kg, respectively, and administered to 3 rats per group. After dosing, blood collection was performed by Jugular vein sampling (by cannula) at 0.25, 0.5, 1, 2, 4, 6, 8, 24 h, and 0.083, 0.25, 0.5, 1, 2, 4, 8, 24h, respectively, followed by centrifugation to obtain plasma. Samples were stored frozen at -80 °C prior to compound extraction and LC-MS/MS analysis. Pharmacokinetic parameters of compounds 103 and 104 in rats were calculated by standard noncompartmental modeling from the systemic plasma concentration-time profile.

[0316] Table B3 shows the mean pharmacokinetic parameters of compounds 103 and 104 in rats (SD; male) determined by the non-compartmental model.

Table B3

PK parameter	Compound			
	103		**104**	
Route	IV	PO	IV	PO
Cl_obs (mL/min/kg)	12.9	ND	8.8	ND
T_{max} (h)	ND	0.25	ND	0.25
C_{max} (ng/mL)	ND	1493	ND	1519
AUC_{last} (h*ng/mL)	1334	1794	1899	2894
F(%)	ND	27.3	ND	30.3

CLAIMS:

1. A compound selected from Table 1, or a pharmaceutically acceptable salt or solvate thereof.

2. A compound selected from Table 2, or a pharmaceutically acceptable salt or solvate thereof.

3. A pharmaceutical composition comprising a compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

4. 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 claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition according to claim 3.

5. The method of claim 4, wherein the LPA-associated disease, disorder, or condition, is a LPA_1-associated disease.

6. The method of claim 4 or 5, wherein the LPA-associated disease, disorder, or condition, is fibrosis, transplant rejection, cancer, osteoporosis, or an inflammatory disorder.

7. The method of claim 6, wherein the fibrosis is pulmonary fibrosis, liver fibrosis, renal fibrosis, cardiac fibrosis, dermal fibrosis, ocular fibrosis, or pancreatic fibrosis.

8. The method of claim 6, 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 or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.

9. The method of claim 4 or 5, 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/126596

A. CLASSIFICATION OF SUBJECT MATTER

C07D 277/62(2006.01)i; C07D 277/02(2006.01)i; C07D 471/04(2006.01)i; A61K 31/426(2006.01)i; A61K 31/428(2006.01)i; A61P 1/16(2006.01)i; A61P 13/12(2006.01)i; A61P 19/10(2006.01)i; A61P 29/00(2006.01)i; A61P 35/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; A61K; A61P

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

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

CNTXT, WPABS, WPABSC, ENTXT, ENTXTC, VCN, VEN, CJFD, CNKI, ISI-WEB OF SCIENCE, PUBMED, BING, STNext: LHOTSE BIO, LEI Hui, ZHANG Qiong, RUVINSKY Anatoly M., lysophosphatidic acid, LPA, Phosphomonoglycerides, Lysophosphoglycerides, fibrosis, transplant rejection, cancer, osteoporosis, inflammatory disorder, 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, multiple sclerosis, Structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2022083703 A1 (LHOTSE BIO, INC. et al.) 28 April 2022 (2022-04-28) claims 1-206, description, the exemplary compounds on pages 68-140	1-9
A	WO 2017223016 A1 (BRISTOL-MYERS SQUIBB COMPANY) 28 December 2017 (2017-12-28) the abstract, claims 1-31, description, lines 10-14 on page 1, line 6 on page 3 to line 5 on page 21	1-9
A	US 2006148830 A1 (ONO PHARMACEUTICAL CO., LTD.) 06 July 2006 (2006-07-06) the abstract, claims 1-76, description, EXAMPLES 62(1)-62(4) on pages 82-83	1-9
A	WO 2020040326 A1 (GACHON UNIVERSITY OF INDUSTRY-ACADEMIC COOPERATION FOUNDATION et al.) 27 February 2020 (2020-02-27) claims 1-10	1-9
A	WO 2021097039 A1 (GILEAD SCIENCES, INC.) 20 May 2021 (2021-05-20) claims 1-129	1-9

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2022	**09 January 2023**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **WAN,Guang** Telephone No. **(86-10)53961859**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/126596

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PALMER, Andreas Marc et al., . "Synthesis and pharmacological evaluation of potential metabolites of the potassium-competitive acid blocker BYK 405879, " *Tetrahedron Letters*, , Vol. 50, 23 April 2009 (2009-04-23), pages 3917-3919	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/126596

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **4-9**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 4-9 relate to methods for treating LPA-associated diseases, disorders, and conditions, and thus do not meet the criteria set out in PCT Rules 39.1(iv). The search report has been carried out and based on the use of the compound of claim 1 or 2, or the pharmaceutical composition according to claim 3 for the manufacturing of a medicament for the treatment of LPA-associated diseases, disorders, and conditions.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2022/126596

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2022083703 A1	28 April 2022	None	
WO 2017223016 A1	28 December 2017	LT 3666771 T	10 December 2021
		IL 263767 A	31 January 2019
		CN 114601830 A	10 June 2022
		HR P20211708 T1	04 February 2022
		PT 3666771 T	27 October 2021
		LT 3472148 T	25 May 2020
		UY 37302 A	02 January 2018
		RS 60347 B1	31 July 2020
		EA 201892710 A1	31 May 2019
		JP 2019518766 A	04 July 2019
		US 2017360759 A1	21 December 2017
		RS 62524 B1	30 November 2021
		SI 3666771 T1	31 December 2021
		MX 2018015563 A	06 June 2019
		US 2021244711 A1	12 August 2021
		HU E049944 T2	30 November 2020
		PE 20190211 A1	07 February 2019
		BR 112018076558 A2	02 April 2019
		NZ 750013 A	25 March 2022
		SI 3472148 T1	31 July 2020
		TW 201808919 A	16 March 2018
		US 2018333395 A1	22 November 2018
		ES 2785951 T3	08 October 2020
		CA 3029202 A1	28 December 2017
		EP 3472148 A1	24 April 2019
		DK 3666771 T3	15 November 2021
		PL 3666771 T3	27 December 2021
		PL 3472148 T3	14 December 2020
		KR 20190020049 A	27 February 2019
		CL 2018003708 A1	08 February 2019
		AR 108838 A1	03 October 2018
		DK 3472148 T3	27 April 2020
		US 2022249443 A1	11 August 2022
		EP 3666771 A1	17 June 2020
		ES 2895385 T3	21 February 2022
		AU 2017281439 A1	07 February 2019
		CO 2019000471 A2	08 February 2019
		US 2020138789 A1	07 May 2020
		AU 2021209334 A1	26 August 2021
		JP 2022106974 A	20 July 2022
		TW 202126629 A	16 July 2021
		ME 03804 B	20 April 2021
		HU E057211 T2	28 April 2022
		CN 109963843 A	02 July 2019
		HR P20200586 T1	10 July 2020
		SG 11201811321T A	30 January 2019
		PT 3472148 T	08 May 2020
		ZA 201808580 B	26 August 2020
		KR 20220038537 A	28 March 2022

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2022/126596

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
US	2006148830	A1	06 July 2006	TW	200408393	A	01 June 2004
				EP	1553075	A1	13 July 2005
				AU	2003241836	A1	23 April 2004
				US	2012088782	A1	12 April 2012
				JP	WO2004031118	A1	09 February 2006
				EP	2565178	A1	06 March 2013
				WO	2004031118	A1	15 April 2004
				US	2008293764	A1	27 November 2008
WO	2020040326	A1	27 February 2020	KR	20200022628	A	04 March 2020
WO	2021097039	A1	20 May 2021	US	2021171500	A1	10 June 2021
				CA	3158743	A1	20 May 2021
				KR	20220101137	A	19 July 2022
				CN	114728168	A	08 July 2022
				TW	202128644	A	01 August 2021
				EP	4058144	A1	21 September 2022
				AU	2020384883	A1	12 May 2022

(19)国家知识产权局

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PCT/CN2022/082072 2022.03.21 CN

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PCT/CN2022/126596 2022.10.21

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WO2023/066359 EN 2023.04.27

(71)申请人 罗特斯生物公司
地址 美国加利福尼亚州

(72)发明人 H·雷 Q·张 A·M·鲁文斯基

(74)专利代理机构 北京坤瑞律师事务所 11494
专利代理师 封新琴

(51)Int.Cl.
C07D 277/62(2006.01)
C07D 277/02(2006.01)
C07D 471/04(2006.01)
A61K 31/426(2006.01)
A61K 31/428(2006.01)
A61P 1/16(2006.01)
A61P 13/12(2006.01)
A61P 19/10(2006.01)
A61P 29/00(2006.01)
A61P 35/00(2006.01)

权利要求书1页 说明书73页

(54)发明名称

用于治疗与LPA受体活性相关的病症的化合物和组合物

(57)摘要

本发明提供了LPA拮抗剂以及包含本文公开的化合物的药物组合物。本发明还提供了用于治疗LPA相关疾病、障碍和病症的方法。

CN 118339149 A

1.一种选自表1的化合物或其药学上可接受的盐或溶剂化物。

2.一种选自表2的化合物或其药学上可接受的盐或溶剂化物。

3.一种药物组合物,所述药物组合物包含根据权利要求1或2所述的化合物或其药学上可接受的盐或溶剂化物以及药学上可接受的载体。

4.一种用于治疗LPA相关疾病、障碍或病症的方法,所述方法包括向有需要的患者施用有效量的根据权利要求1或2所述的化合物或其药学上可接受的盐或溶剂化物,或根据权利要求3所述的药物组合物。

5.根据权利要求4所述的方法,其中所述LPA相关疾病、障碍或病症是LPA_1相关疾病。

6.根据权利要求4或5所述的方法,其中所述LPA相关疾病、障碍或病症是纤维化、移植排斥、癌症、骨质疏松症或炎性障碍。

7.根据权利要求6所述的方法,其中所述纤维化是肺纤维化、肝纤维化、肾脏纤维化、心脏纤维化、皮肤纤维化、眼纤维化或胰腺纤维化。

8.根据权利要求6所述的方法,其中所述癌症是膀胱、血液、骨骼、脑、乳腺、中枢神经系统、子宫颈、结肠、子宫内膜、食管、胆囊、生殖器、泌尿生殖道、头、肾、喉、肝、肺、肌肉组织、颈、口腔粘膜或鼻粘膜、卵巢、胰腺、前列腺、皮肤、脾、小肠、大肠、胃、睾丸或甲状腺的癌症。

9.根据权利要求4或5所述的方法,其中所述LPA相关疾病、障碍或病症是特发性肺纤维化(IPF)、非酒精性脂肪性肝炎(NASH)、非酒精性脂肪性肝病(NAFLD)、慢性肾脏病、糖尿病肾病、系统性硬化病、COVID-19、慢性阻塞性肺疾病(COPD)、神经炎症或多发性硬化。

用于治疗与LPA受体活性相关的病症的化合物和组合物

相关申请的交叉引用

[0001] 本申请要求于2022年3月21日提交的国际专利申请号PCT/CN2022/082072;以及2021年10月21日提交的国际专利申请号PCT/CN2021/125409的权益,将其中的每一个专利申请通过引用以其整体并入本文。

技术领域

[0002] 本公开文本提供了LPA拮抗剂以及包含本文公开的化合物的药物组合物。还提供了用于治疗LPA相关疾病、障碍和病症的方法。

背景技术

[0003] 各种脂质介质(包括类二十烷酸和血小板活化因子(PAF))由来自细胞膜的磷脂酶的活性产生。溶血磷脂是一类膜源性生物活性脂质介质并且包括溶血磷脂酸(LPA)。LPA不是单分子实体,而是具有不同长度和饱和度的脂肪酸的内源性结构变体的集合。LPA影响包括细胞增殖、分化、存活、迁移、粘附、侵袭和形态发生的细胞功能。这些功能影响包括神经发生、血管生成、伤口愈合、免疫和肿瘤发生的许多生物过程。LPA具有作为生物效应分子的作用,并且具有广泛的生理作用(如但不限于对血压、血小板活化和平滑肌收缩的影响),以及多种细胞效应,所述细胞效应包括细胞生长、细胞变圆、神经突回缩和肌动蛋白应力纤维形成和细胞迁移。LPA的效应主要是受体介导的。用LPA激活LPA受体(LPA_1、LPA_2、LPA_3、LPA_4、LPA_5、LPA_6)介导一系列下游信号传导级联。

发明内容

[0004] 拮抗性LPA受体(如LPA_1受体)可以用于治疗多种障碍,包括纤维化(如肺纤维化、肝纤维化、肾纤维化、动脉纤维化和系统性硬化病)、以及因此由纤维化引起的疾病(例如,肺纤维化(例如,特发性肺纤维化(IPF))、肝纤维化(包括非酒精性脂肪性肝炎(NASH))、肾脏纤维化(如糖尿病性肾病)、系统性硬化病-硬皮病等)、COVID-19、慢性阻塞性肺疾病(COPD)、神经炎症或多发性硬化。本申请描述了LPA拮抗剂以及包含本文公开的化合物的药物组合物。还提供了用于治疗LPA相关疾病、障碍和病症的方法。

[0005] 在一个实施方案中,提供了表1的化合物或其药学上可接受的盐或溶剂化物。在一个实施方案中,提供了表2的化合物或其药学上可接受的盐、溶剂化物、立体异构体或立体异构体的混合物。

[0006] 本文还提供了药物组合物,所述药物组合物包含表1的化合物或其药学上可接受的盐或溶剂化物以及药学上可接受的赋形剂。

[0007] 本文还提供了用于治疗或预防有需要的受试者的LPA相关疾病的方法,所述方法包括向受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或其药物组合物。在一些实施方案中,所述LPA相关疾病是LPA_1相关疾病,如但不限于纤维化、移植排斥、癌症、骨质疏松症或炎性障碍。

[0008] 在一些实施方案中,所述LPA相关疾病是纤维化、移植排斥、癌症、骨质疏松症或炎性障碍。在这些实施方案中的某些中,所述纤维化是肺、肝、肾、心脏、皮肤、眼或胰腺纤维化。在某些实施方案中,所述癌症是膀胱、血液、骨骼、脑、乳腺、中枢神经系统、子宫颈、结肠、子宫内膜、食管、胆囊、生殖器、泌尿生殖道、头、肾、喉、肝、肺、肌肉组织、颈、口腔粘膜或鼻粘膜、卵巢、胰腺、前列腺、皮肤、脾、小肠、大肠、胃、睾丸或甲状腺的癌症。

[0009] 在一些实施方案中,所述LPA相关疾病是特发性肺纤维化(IPF)、非酒精性脂肪性肝炎(NASH)、非酒精性脂肪性肝病(NAFLD)、慢性肾脏病、糖尿病肾病、系统性硬化病、COVID-19、慢性阻塞性肺疾病(COPD)、神经炎症或多发性硬化。

[0010] 本文还提供了用于治疗或预防有需要的受试者的纤维化的方法,所述方法包括向受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或其药学上可接受盐或溶剂化物或其药物组合物。

[0011] 在一些实施方案中,所述纤维化是特发性肺纤维化(IPF)、非酒精性脂肪性肝炎(NASH)、慢性肾脏病、糖尿病肾病和系统性硬化病。例如,所述纤维化可以是IPF。

具体实施方式

定义

[0012] 以下描述阐述了本发明技术的示例性实施方案。然而,应认识到,这样的描述并不旨在作为对本公开文本的范围的限制,而是旨在作为示例性实施方案的描述而提供。

[0013] 如在本说明书中所用,以下词语、短语和符号通常旨在具有如下文所阐述的含义,但使用它们的上下文另有说明除外。

[0014] 如本文所用,术语“化合物”意在包括所描绘结构的所有立体异构体、几何异构体、互变异构体和同位素。除非另外说明,否则本文中通过名称或结构鉴别为一种特定互变异构体形式的化合物旨在包括其他互变异构体形式。

[0015] 化合物中的一些以互变异构体存在。互变异构体彼此处于平衡。例如,含有酰胺的化合物可以与亚氨酸互变异构体平衡地存在。无论显示哪种互变异构体,并且无论互变异构体之间的平衡性质如何,本领域普通技术人员都将化合物理解为包括酰胺和亚氨酸互变异构体两者。因此,含有酰胺的化合物应理解为包括它们的亚氨酸互变异构体。同样,含有亚氨酸的化合物应理解为包括它们的酰胺互变异构体。

[0016] 本文得到的任何化合物或结构也旨在表示化合物的未标记的形式以及同位素标记的形式。这些形式的化合物也可以称为“同位素富集的类似物”。同位素标记的化合物具有由本文描绘的结构,除了一个或多个原子被具有选定的原子质量或质量数的原子替代。可以并入所公开的化合物的同位素的例子分别包括氢、碳、氮、氧、磷、氟、氯以及碘的同位素,如^{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以及^{125}I。本公开文本的各种同位素标记的化合物,例如掺入放射性同位素(如^{3}H和^{14}C)的化合物。此类同位素标记的化合物可以用于代谢研究、反应动力学研究、检测或成像技术(如正电子发射断层扫描术(PET)或单光子发射计算机断层扫描术(SPECT),包括药物或基底组织分布测定)中,或者用于患者的放射性治疗中。

[0017] 术语“同位素富集的类似物”包括本文所述的化合物的“氘代类似物”,其中一个或多个氢被氘替代(如碳原子上的氢)。这些化合物展现出增加的代谢抗性,并且因此当施用

于哺乳动物(特别是人时)可用于增加任何化合物的半衰期。参见例如,Foster,“Deuterium Isotope Effects in Studies of Drug Metabolism,”Trends Pharmacol.Sci.5(12):524-527(1984)。此类化合物通过本领域熟知的手段来合成,例如通过采用一个或多个氢已经被氘替代的起始材料来合成。

[0018] 本公开文本的氘标记或取代的治疗化合物可以具有改善的DMPK(药物代谢和药代动力学)特性,涉及分布、代谢和排泄(ADME)。用较重的同位素如氘取代因为代谢稳定性更高而可以提供某些治疗优势,例如体内半衰期延长、剂量需求减少和/或治疗指数改善。^{18}F、^{3}H、^{11}C标记的化合物可以用于PET或SPECT或其他成像研究。本公开文本的同位素标记的化合物及其前药通常可以通过用容易获得的同位素标记的试剂取代非同位素标记的试剂,通过实施在方案中或在下述的实施例和制备中公开的程序来制备。应当理解,在此上下文中的氘被认为是本文所述的化合物中的取代基。

[0019] 这种较重同位素(特别是氘)的浓度可以通过同位素富集因子来定义。在本公开文本的化合物中,未特别指定为特定同位素的任何原子意在代表所述原子的任何稳定同位素。除非另有说明,否则当位置被具体指定为“H”或“氢”时,所述位置应理解为具有其天然丰度同位素组成的氢。因此,在本公开文本的化合物中,被具体指定为氘(D)的任何原子意在代表氘。

[0020] 在许多情况下,由于存在氨基和/或羧基或与其类似的基团,本公开文本的化合物能够形成酸性和/或碱性盐。

[0021] 还提供了本文所述化合物的药学上可接受的盐、水合物、溶剂化物、互变异构形式、多晶型物和前药。“药学上可接受的”或“生理学上可接受的”是指可用于制备适合于兽医或人药物用途的药物组合物的化合物、盐、组合物、剂型和其他材料。

[0022] 术语给定化合物的“药学上可接受的盐”是指保留给定化合物的生物有效性和特性并且在生物学上或其他方面不是不合需要的盐。“药学上可接受的盐”或“生理学上可接受的盐”包括例如与无机酸形成的盐和与有机酸形成的盐。另外,如果作为酸加成盐获得本文描述的化合物,则可以通过将酸式盐的溶液碱化来获得游离碱。相反,如果产物是游离碱,则可以按照用于从碱化合物制备酸加成盐的常规程序,通过将游离碱溶解在合适的有机溶剂中并且用酸处理所述溶液来产生加成盐(特别是药学上可接受的加成盐)。本领域技术人员将认识到可用于制备无毒的药学上可接受的加成盐的各种合成方法。药学上可接受的酸加成盐可以由无机酸和有机酸制备。衍生自无机酸的盐包括例如盐酸、氢溴酸、硫酸、硝酸、磷酸等。衍生自有机酸的盐包括例如乙酸、丙酸、葡萄糖酸、乙醇酸、丙酮酸、草酸、苹果酸、丙二酸、琥珀酸、马来酸、富马酸、酒石酸、柠檬酸、苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、对甲苯磺酸、水杨酸等。同样,药学上可接受的碱加成盐可以由无机碱和有机碱制备。仅举例来说,衍生自无机碱的盐包括钠盐、钾盐、锂盐、铝盐、铵盐、钙盐和镁盐。衍生自有机碱的盐包括但不限于NH_3、或伯胺、仲胺、叔胺的盐,如衍生自含N杂环、含N杂芳基或衍生自式$N(R^N)_3$的胺(例如,$HN^+(R^N)_3$或(烷基)$N^+(R^N)_3$)的盐,其中每个R^N独立地是氢、烷基、烯基、炔基、卤代烷基、环烷基、杂环基、芳基或杂芳基,其中各自任选地被取代,如被一个或多个(例如,1-5个或1-3个)取代基(例如,卤代基、氰基、羟基、氨基、烷基、烯基、炔基、卤代烷基、烷氧基或卤代烷氧基)取代。仅举例来说,合适的胺的具体例子包括异丙胺、三甲基胺、二乙基胺、三(异丙基)胺、三(正丙基)胺、乙醇胺、2-二甲基氨基乙醇、哌嗪、哌啶、吗啉、N-乙基哌

啶等。

[0023] 术语“取代的”意指在指定原子或基团上的任一个或多个氢原子被一个或多个不是氢的取代基替代,条件是不超过指定原子的正常化合价。所述一个或多个取代基包括但不限于烷基、烯基、炔基、烷氧基、酰基、氨基、酰胺基、脒基、芳基、叠氮基、氨基甲酰基、羧基、羧基酯、氰基、胍基、卤代基、卤代烷基、卤代烷氧基、杂烷基、杂芳基、杂环基、羟基、肼基、亚氨基、氧代基、硝基、烷基亚磺酰基、磺酸、烷基磺酰基、硫氰酸酯、硫醇、硫酮或其组合。

[0024] 通过定义具有无限附加的其他取代基的取代基而得到的聚合物或类似的不定结构(例如,具有取代的烷基的取代的芳基,所述取代的烷基自身被取代的芳基取代,所述取代的芳基进一步被取代的杂烷基取代,等)并不旨在包括在本文中。除非另有说明,否则本文所述的化合物中的最大连续取代数为三。例如,被两个其他取代的芳基取代的芳基的连续取代限于((取代的芳基)取代的芳基)取代的芳基。类似地,以上定义不旨在包括不允许的取代模式(例如,被5个氟或具有两个相邻氧环原子的杂芳基取代的甲基)。此类不允许的取代模式是技术人员熟知的。当用于修饰化学基团时,术语“取代的”可以描述本文定义的其他化学基团。除非另有说明,否则当基团被描述为任选取代的时,所述基团的任何取代基本身是未取代的。例如,在一些实施方案中,术语“取代的烷基”是指具有一个或多个取代基的烷基,所述一个或多个取代基包括羟基、卤代基、烷氧基、环烷基、杂环基、芳基和杂芳基。在其他实施方案中,所述一个或多个取代基可以进一步被卤代基、烷基、卤代烷基、羟基、烷氧基、环烷基、杂环基、芳基或杂芳基取代,其中每一个都是取代的。在其他实施方案中,取代基可以进一步被卤代基、烷基、卤代烷基、烷氧基、羟基、环烷基、杂环基、芳基或杂芳基取代,其中每一个都是未取代的。

[0025] 术语“任选的”或“任选地”意指随后描述的事件或情况可以发生或者可以不发生,并且所述描述包括发生所述事件或情况的情形和不发生所述事件或情况的情形。此外,术语“任选地经取代”是指指定原子或基团上的任何一个或多个氢原子可以或可以不被除氢之外的部分替代。

[0026] 不位于两个字母或符号之间的划线(“-”)用于指示取代基的附接点。例如,-C(O)NH_2是通过碳原子附接。化学基团前端或末端的划线是为了方便起见;化学基团可以用或不用一个或多个划线描绘,而不丧失它们的普通含义。在结构中通过线绘制的波浪线指示基团的附接点。除非在化学或结构上要求,否则书写或命名化学基团的顺序不指示或暗示方向性。

[0027] 前缀“C_{u-v}”指示以下基团具有u至v个碳原子。例如,“C_{1-6}烷基”指示烷基具有1至6个碳原子。

[0028] 本文提及“约”某一值或参数时包括(并描述)涉及该值或参数本身的实施方案。在某些实施方案中,术语“约”包括所指示的量±10%。在其他实施方案中,术语“约”包括所指示的量±5%。在某些其他实施方案中,术语“约”包括所指示的量±1%。此外,关于术语“约X”包括对“X”的描述。此外,除非上下文另有明确规定,否则单数形式“一个/一种”和“所述”包括复数指示物。因此,例如,提及“所述化合物”包括多种此类化合物,并且提及“所述测定”包括提及本领域技术人员已知的一种或多种测定及其等效物。

[0029] “烷基”是指未支化或支化的饱和烃链。如本文所用,烷基具有1至20个碳原子(即,

C_{1-20}烷基)、1至12个碳原子(即,C_{1-12}烷基)、1至8个碳原子(即,C_{1-8}烷基)、1至6个碳原子(即,C_{1-6}烷基)或1至4个碳原子(即,C_{1-4}烷基)。烷基的例子包括例如甲基、乙基、丙基、异丙基、正丁基、仲丁基、异丁基、叔丁基、戊基、2-戊基、异戊基、新戊基、己基、2-己基、3-己基和3-甲基戊基。当具有特定碳数的烷基残基通过化学名称来命名或通过分子式来标识时,具有该碳数的所有位置异构体都可以涵盖在内;因此,例如,"丁基"包括正丁基(即,$-(CH_2)_3CH_3$)、仲丁基(即,$-CH(CH_3)CH_2CH_3$)、异丁基(即,$-CH_2CH(CH_3)_2$)和叔丁基(即,$-C(CH_3)_3$),并且"丙基"包括正丙基(即,$-(CH_2)_2CH_3$)和异丙基(即,$-CH(CH_3)_2$)。

[0030] "烯基"是指这样的烷基,其含有至少一个(例如,1-3个或1个)碳-碳双键,并且具有从2至20个碳原子(即,C_{2-20}烯基)、2至12个碳原子(即,C_{2-12}烯基)、2至8个碳原子(即,C_{2-8}烯基)、2至6个碳原子(即,C_{2-6}烯基)或2至4个碳原子(即,C_{2-4}烯基)。烯基的例子包括例如,乙烯基、丙烯基、丁二烯基(包括1,2-丁二烯基和1,3-丁二烯基)。

[0031] "炔基"是指这样的烷基,其含有至少一个(例如,1-3个或1个)碳-碳三键,并且具有从2至20个碳原子(即,C_{2-20}炔基)、2至12个碳原子(即,C_{2-12}炔基)、2至8个碳原子(即,C_{2-8}炔基)、2至6个碳原子(即,C_{2-6}炔基)或2至4个碳原子(即,C_{2-4}炔基)。术语"炔基"还包括具有一个三键和一个双键的那些基团。

[0032] 可以使用某些常用的可替代的化学名称。例如,二价基团如二价"烷基"基团、二价"芳基"基团等也可以分别称为"亚烷基(alkylene)"基团(或"alkyleny1"基团)、"亚芳基(arylene)"基团(或"aryleny1"基团)。

[0033] "烷氧基"是指基团"烷基-O-"。烷氧基的例子包括例如甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、叔丁氧基、仲丁氧基、正戊氧基、正己氧基和1,2-二甲基丁氧基。

[0034] "卤代烷基"是指如上定义的无支链烷基或支链烷基,其中一个或多个(例如,1至6个或1至3个)氢原子被卤素替代。例如,在残基被超过一个卤素取代的情况下,它可以通过使用对应于所附接的卤素部分的数量的前缀来提及。二卤代烷基和三卤代烷基是指被两个("二")或三个("三")卤代基取代的烷基,所述卤代基可以是但不一定是相同的卤素。卤代烷基的例子包括例如三氟甲基、二氟甲基、氟甲基、三氯甲基、2,2,2-三氟乙基、1,2-二氟乙基、3-溴-2-氟丙基、1,2-二溴乙基等。

[0035] "卤代烷氧基"是指如上定义的烷氧基,其中一个或多个(例如,1至6个或1至3个)氢原子被卤素替代。

[0036] "羟基烷基"是指如上文所定义的烷基,其中一个或多个(例如,1至6个或1至3个)氢原子被羟基替代。

[0037] "烷硫基"是指基团"烷基-S-"。

[0038] "酰基"是指基团-C(O)R,其中R是氢、烷基、环烷基、杂环基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代。酰基的例子包括甲酰基、乙酰基、环己基羰基、环己基甲基-羰基和苯甲酰基。

[0039] "酰胺基"是指"C-酰胺基"基团(其是指基团$-C(O)NR^yR^z$)和"N-酰胺基"基团(其是指基团$-NR^yC(O)R^z$),其中R^y和R^z独立地是氢、烷基、烯基、炔基、环烷基、杂环基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代,或R^y和R^z一起形成环烷基或杂环基;如本文所定义,其中每一个可以任选地被取代。

[0040] "氨基"是指基团$-NR^yR^z$,其中R^y和R^z独立地是氢、烷基、烯基、炔基、环烷基、杂环

基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代。

[0041] "脒基"是指-C(NR^{y})(NR$^{z}_{2}$),其中R^{y}和R^{z}独立地是氢、烷基、烯基、炔基、环烷基、杂环基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代。

[0042] "芳基"是指具有单环(例如,单环)或多环(例如,双环或三环)的芳香族碳环基团,包括稠合体系。如本文所用,芳基具有6至20个环碳原子(即,C_{6-20}芳基)、6至12个碳环原子(即,C_{6-12}芳基)、或6至10个碳环原子(即,C_{6-10}芳基)。芳基的例子包括例如苯基、萘基、茚基和蒽基。然而,芳基不以任何方式涵盖下文所定义的杂芳基或与下文所定义的杂芳基重叠。如果一个或多个芳基与杂芳基稠合,则所得的环体系是杂芳基,而不管附接点如何。如果一个或多个芳基与杂环基稠合,则所得的环体系是杂环基,而不管附接点如何。如果一个或多个芳基与环烷基稠合,则所得的环体系是环烷基,而不管附接点如何。

[0043] "氨基甲酰基"是指"O-氨基甲酰基"基团,其是指-O-C(O)NR^{y}R^{z}基团;和"N-氨基甲酰基"基团,其是指-NR^{y}C(O)OR^{z}基团,其中R^{y}和R^{z}独立地是氢、烷基、烯基、炔基、环烷基、杂环基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代。

[0044] "羧基酯"或"酯"是指-OC(O)R^{x}和-C(O)OR^{x}二者,其中R^{x}是烷基、烯基、炔基、环烷基、杂环基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代。

[0045] "环烷基"是指具有单个环或多个环的饱和或部分不饱和的环状烷基,包括稠合、桥接和螺环体系。术语"环烷基"包括环烯基(即,具有至少一个双键的环状基团)和具有至少一个sp^{3}碳原子的碳环稠环体系(即,至少一个非芳族环)。如本文所用,环烷基具有3至20个环碳原子(即,C_{3-20}环烷基)、3至14个环碳原子(即,C_{3-14}环烷基)、3至12个环碳原子(即,C_{3-12}环烷基)、3至10个环碳原子(即,C_{3-10}环烷基)、3至8个环碳原子(即C_{3-8}环烷基)或3至6个环碳原子(即,C_{3-6}环烷基)。单环基团包括例如环丙基、环丁基、环戊基、环己基、环庚基和环辛基。多环基团包括例如,双环[2.2.1]庚基、双环[2.2.2]辛基、金刚烷基、降冰片基、十氢萘基、7,7-二甲基-双环[2.2.1]庚基等。此外,术语环烷基旨在涵盖可以与芳基环稠合的任何非芳族环,而不管与分子的其余部分的附接情况如何。此外,当在相同碳原子上具有两个取代位置时,环烷基还包括"螺环烷基",例如螺[2.5]辛基、螺[4.5]癸基、或螺[5.5]十一烷基。

[0046] "亚氨基"是指基团-C(NR^{y})R^{z},其中R^{y}和R^{z}各自独立地是氢、烷基、烯基、炔基、环烷基、杂环基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代。

[0047] "卤素"或"卤代基"是指占据周期表VIIA族的原子,如氟、氯、溴或碘。

[0048] "杂烷基"是指烷基,其中一个或多个碳原子(和任何相关的氢原子)各自独立地被相同或不同的杂原子基团替代。术语"杂烷基"包括具有碳和杂原子的无支链的饱和链或支链饱和链。举例来说,1、2或3个碳原子可以独立地被相同或不同的杂原子基团替代。杂原子基团包括但不限于-NR-、-O-、-S-、-S(O)-、-S(O)$_{2}$-等,其中R是H、烷基、芳基、环烷基、杂烷基、杂芳基或杂环基,其中每一个可以任选地被取代。杂烷基的例子包括-OCH$_{3}$、-CH$_{2}$OCH$_{3}$、-SCH$_{3}$、-CH$_{2}$SCH$_{3}$、-NRCH$_{3}$和-CH$_{2}$NRCH$_{3}$,其中R是氢、烷基、芳基、芳基烷基、杂烷基或杂芳基,其中每一个可以任选地被取代。如本文所用,杂烷基包括1至10个碳原子、1至8个碳原子或1至4个碳原子;以及1至3个杂原子、1至2个杂原子或1个杂原子。

[0049] "杂芳基"是指具有单环或多个稠环的芳族基团,其中一个或多个环杂原子独立地选自氮、氧和硫。如本文所用,杂芳基包括1至20个环碳原子(即,C_{1-20}杂芳基)、3至12个环碳

原子(即,C_{3-12}杂芳基)或3至8个碳环原子(即,C_{3-8}杂芳基),以及1至5个环杂原子、1至4个环杂原子、1至3个环杂原子、1至2个环杂原子或1个环杂原子,所述环杂原子独立地选自氮、氧和硫。在某些情况下,杂芳基包括5-10元环体系、5-7元环体系或5-6元环体系,各自独立地具有1至4个环杂原子、1至3个环杂原子、1至2个环杂原子或1个环杂原子,所述环杂原子独立地选自氮、氧和硫。杂芳基的例子包括例如,吖啶基、苯并咪唑基、苯并噻唑基、苯并吲哚基、苯并呋喃基、苯并噻唑基、苯并噻二唑基、苯并萘并呋喃基、苯并噁唑基、苯并噁唑基、苯并噻吩基(benzothienyl/benzothiophenyl)、苯并三唑基、苯并[4,6]咪唑并[1,2-a]吡啶基、咔唑基、噌啉基、二苯并呋喃基、二苯并噻吩基、呋喃基、异噻唑基、咪唑基、吲唑基、吲哚基、吲唑基、异吲哚基、异喹啉基、异噁唑基、萘啶基、噁二唑基、噁唑基、1-氧吡啶基、1-氧化嘧啶基、1-氧化吡嗪基、1-氧化哒嗪基、吩嗪基、酞嗪基、喋啶基、嘌呤基、吡咯基、吡唑基、吡啶基、吡嗪基、嘧啶基、哒嗪基、喹唑啉基、喹喔啉基、喹啉基、奎宁环基、异喹啉基、噻唑基、噻二唑基、三唑基、四唑基和三嗪基。稠合杂芳基环的例子包括但不限于苯并[d]噻唑基、喹啉基、异喹啉基、苯并[b]苯硫基、吲唑基、苯并[d]咪唑基、吡唑并[1,5-a]吡啶基和咪唑并[1,5-a]吡啶基,其中杂芳基可以经由稠合体系的任一环结合。具有含有至少一个杂原子的单个或多个稠环的任何芳族环被认为是杂芳基,而不管与分子其余部分的附接情况(即,通过任何一个稠环)如何。杂芳基不涵盖如上定义的芳基或与如上定义的芳基重叠。

[0050] “杂环基”是指饱和或部分不饱和的环状烷基,其中一个或多个环杂原子独立地选自氮、氧和硫。术语“杂环基”包括杂环烯基(即,具有至少一个双键的杂环基)、桥接的杂环基、稠合的杂环基基团和螺杂环基。杂环基可以是单环或多环,其中多环可以是稠合的、桥接的或螺环,并且可以包括一个或多个(例如,1至3个)氧代(=O)或N-氧化物(-O-)部分。含有至少一个杂原子的任何非芳族环被认为是杂环基,而不管附接情况(即,可以通过碳原子或杂原子结合)如何。此外,术语杂环基旨在涵盖含有至少一个杂原子的任何非芳族环,所述环可以与环烷基、芳基或杂芳基环稠合,而不管与分子其余部分的附接情况如何。如本文所用,杂环基具有2至20个环碳原子(即,C_{2-20}杂环基)、2至12个环碳原子(即,C_{2-12}杂环基)、2至10个环碳原子(即,C_{2-10}杂环基)、2至8个环碳原子(即,C_{2-8}杂环基)、3至12个环碳原子(即,C_{3-12}杂环基)、3至8个环碳原子(即,C_{3-8}杂环基)、或3至6个环碳原子(即,C_{3-6}杂环基);具有1至5个环杂原子、1至4个环杂原子、1至3个环杂原子、1至2个环杂原子、或1个环杂原子,所述环杂原子独立地选自氮、硫或氧。杂环基的例子包括例如氮杂环丁烷基、氮杂环庚三烯基、苯并二氧杂环戊烯基、苯并[b][1,4]二氧杂环庚三烯基、1,4-苯并二噁烷基、苯并吡喃基、苯并二噁英基、苯并吡喃酮基、苯并呋喃酮基、二氧戊环基、二氢吡喃基、氢吡喃基、噻吩基[1,3]二噻烷基、十氢异喹啉基、呋喃酮基、咪唑啉基、咪唑烷基、吲哚啉基、吲哚嗪基、异吲哚啉基、异噻唑烷基、异噁唑烷基、吗啉基、八氢吲哚基、八氢异吲哚基、2-氧代哌嗪基、2-氧代哌啶基、2-氧代吡咯烷基、噁唑烷基、环氧乙烷基、氧杂环丁烷基、吩噻嗪基、吩噁嗪基、哌啶基、哌嗪基、4-哌啶酮基、吡咯烷基、吡唑烷基、奎宁环基、噻唑烷基、四氢呋喃基、四氢吡喃基、三噻烷基、四氢喹啉基、噻吩基(thiophenyl)(即,噻吩基(thienyl))、硫代吗啉基、硫杂吗啉基、1-氧代-硫代吗啉基和1,1-二氧代-硫代吗啉基。当在相同碳原子上有两个取代位置时,术语“杂环基”还包括“螺杂环基”。螺杂环基环的例子包括例如双环的环体系和三环的环体系,如氧杂双环[2.2.2]辛烷基、2-氧杂-7-氮杂螺[3.5]壬基、2-氧杂-6-氮杂螺[3.4]辛基和6-氧杂-1-氮杂螺[3.3]庚基。稠合杂环基环的例子包括但不限于1,2,3,

4-四氢异喹啉基、4,5,6,7-四氢噻吩并[2,3-c]吡啶基、吲哚啉基和异吲哚啉基,其中杂环基可以经由稠合体系的任一环结合。

[0051] “磺酰基”是指基团-S(O)$_2$R^y,其中R^{y}是氢、烷基、烯基、炔基、环烷基、杂环基、芳基、杂烷基或杂芳基;如本文所定义,其中每一个可以任选地被取代。磺酰基的例子是甲基磺酰基、乙基磺酰基、苯基磺酰基和甲苯磺酰基。

[0052] “烷基磺酰基”是指基团-S(O)$_2$R,其中R是烷基。

[0053] “烷基亚磺酰基”是指基团-S(O)R,其中R是烷基。

[0054] 如本文所用,“药学上可接受的载体”或“药学上可接受的赋形剂”包括任何和所有溶剂、分散介质、包衣、抗细菌剂和抗真菌剂、等渗和吸收延迟剂等。此类介质和药剂用于药物活性物质的用途在本领域是熟知的。除非任何常规介质或药剂与活性成分不相容,否则考虑其在治疗组合物中的用途。还可以将补充性活性成分并入组合物中。

[0055] “溶剂化物”是通过溶剂与化合物的相互作用形成的。还提供了本文所述化合物的盐的溶剂化物。还提供了本文所述化合物的水合物。

[0056] 如本文所用的术语“LPA相关疾病”意指包括但不限于这样的疾病、障碍或病症,其中通过LPA激活至少一种LPA受体促成疾病、障碍或病症的症候或进展。这些疾病、障碍或病症可以由遗传、医源性、免疫、感染、代谢、肿瘤、毒性、外科和/或创伤病因中的一种或多种引起。因此,抑制一种或多种溶血磷脂酸(LPA)受体(例如,LPA$_1$、LPA$_2$、LPA$_3$、LPA$_4$、LPA$_5$或LPA$_6$受体)信号传导可以改变疾病、障碍或病症的病状和/或症状和/或进展。在一些实施方案中,LPA相关疾病是LPA1相关疾病,其中调制LPA1受体信号传导可以改变疾病、障碍或病症的病理和/或症状和/或进展。

[0057] 如本文所用,术语“纤维化”或“纤维化障碍”是指与细胞和/或纤连蛋白和/或胶原蛋白的异常积累和/或成纤维细胞募集增加相关的病症,包括但不限于个体器官或组织(如心脏、肾、肝、关节、肺、胸膜组织、腹膜组织、皮肤、角膜、视网膜、肌肉骨骼和消化道)的纤维化。

[0058] 如本文所用,术语“药学上可接受的”指示化合物或其盐或组合物在化学上和/或毒理学上与构成配制品的其他成分和/或用其治疗的受试者相容。

[0059] 术语“施用(administration)”或“施用(administering)”是指将一定剂量的化合物或药物组合物给与脊椎动物或无脊椎动物(包括哺乳动物、鸟、鱼或两栖动物)的方法。施用方法可以根据各种因素而变,例如药物组合物的组分、疾病的部位以及疾病的严重程度。

[0060] 如本文所用,术语“有效量”或“有效剂量”或“药学上有效量”或“治疗有效量”是指所施用的足够量的化学实体(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物),所述量将在一定程度上缓解所治疗的疾病或病症的一或多种症状,并且可以包括治愈疾病。“治愈”意指活动性疾病的症状被消除。结果包括疾病的体征、症状或原因的减少和/或减轻或生物系统的任何其他希望的改变。例如,针对治疗用途的“有效量”是提供临床上显著的疾病症状降低所需的包含如本文公开的化合物的组合物的量。在任何单独情况下的适当“有效”量是使用任何合适技术确定,如剂量递增研究。在一些实施方案中,如本文所提供的化合物的“治疗有效量”是指作为单药疗法或组合疗法有效的化合物的量。

[0061] 术语“赋形剂”或“药学上可接受的赋形剂”意指药学上可接受的材料、组合物或媒介物,如液体或固体填充剂、稀释剂、载体、溶剂或包囊材料。在一些实施方案中,各组分在

与药物配制品的其他成分相容并且适合于与人和动物的组织或器官接触而无过度毒性、刺激、过敏反应、免疫原性或其他问题或并发症,与合理的益处/风险比相称的意义上是“药学上可接受的”。参见例如,Remington:The Science and Practice of Pharmacy,第21版;Lippincott Williams&Wilkins:Philadelphia,PA,2005;Handbook of Pharmaceutical Excipients,第6版;Rowe等人编辑;The harmaceutical Press and the American Pharmaceutical Association:2009;Handbook of Pharmaceutical Additives,第3版;Ash和Ash编辑;Gower Publishing Company:2007;Pharmaceutical Preformulation and Formulation,第2版;Gibson编辑;CRC Press LLC:Boca Raton,FL,2009。

[0062] 术语“药物组合物”是指本文公开的化合物,或本文提供的其药学上可接受的盐或溶剂化物与其他化学成分(在本文中统称为“赋形剂”)(如载体、稳定剂、稀释剂、分散剂、助悬剂和/或增稠剂)的混合物。药物组合物有助于将化合物施用于生物体。本领域中存在多种施用化合物的技术,包括但不限于直肠、口服、静脉内、气雾剂、肠胃外、眼部、肺部和外用施用。

[0063] 在治疗疾病、障碍或病症的上下文中,术语“治疗(treat、treating和treatment)”意在包括缓解或根除障碍、疾病或病症或与所述障碍、疾病或病症相关的一种或多种症状;或减缓疾病、障碍或病症或其一种或多种症状的进展、扩散或恶化。

[0064] 如本文所用,术语“预防”是完全或部分预防如本文所述的疾病或病症或其症状的发作、复发或扩散。

[0065] 如本文所用,术语“受试者”、“患者”或“个体”可互换使用并且是指任何动物,包括哺乳动物,如小鼠、大鼠、其他啮齿动物、兔、犬、猫、猪、牛、绵羊、马、灵长类动物和人。在一些实施方案中,术语是指希望或需要诊断、预后或疗法的受试者,特别是指哺乳动物受试者。在一些实施方案中,受试者是人。在一些实施方案中,受试者已经历和/或展现出待治疗和/或预防的疾病、障碍或病症的至少一种症状。

[0066] 术语“治疗方案”和“给药方案”可互换地使用以指代组合中每种治疗剂的施用剂量和时间。

[0067] 如本文所用,术语“药物组合”是指由多于一种活性成分的混合或组合产生的药物治疗,并且包括活性成分的固定组合和非固定组合两者。

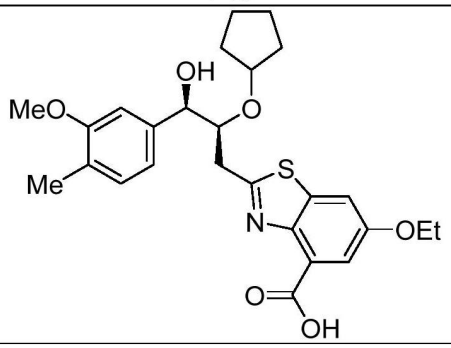
[0068] 如本文所用,术语“组合疗法”是指两种不同治疗活性剂(即,组合的组分或组合配偶物)的给药方案,其中治疗活性剂以医护人员规定的方式或根据如本文定义的管理机构一起或分开施用。

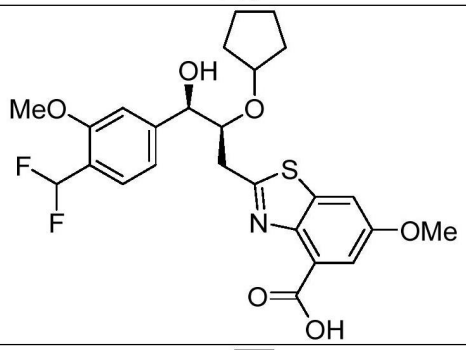
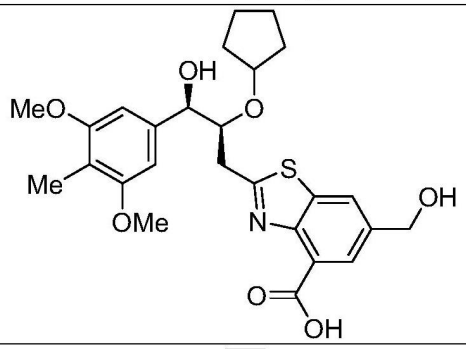
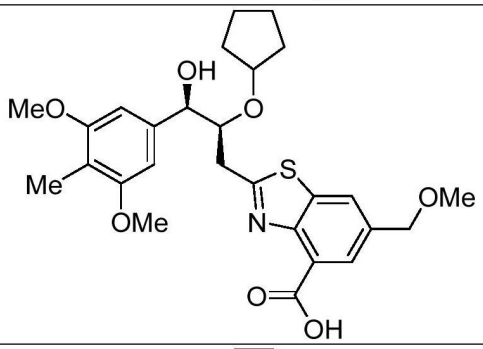
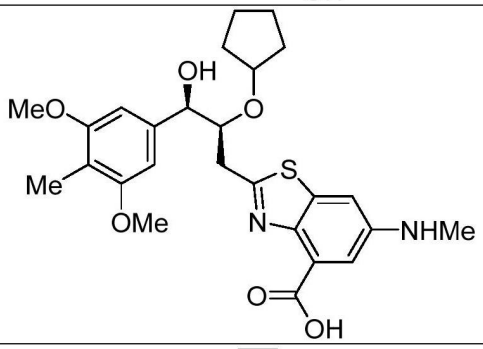
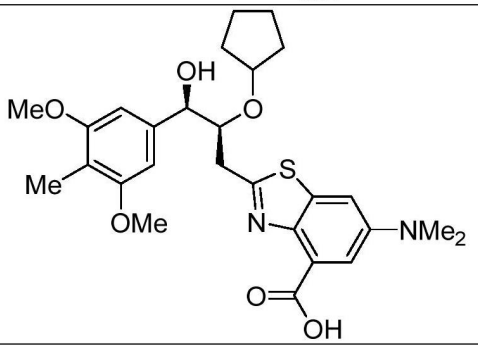
[0069] 如本文所用,术语“调节(modulate、modulating或modulation)”是指调控或调整(例如,增加或减少),并且可以包括例如激动作用、部分激动作用或拮抗作用。

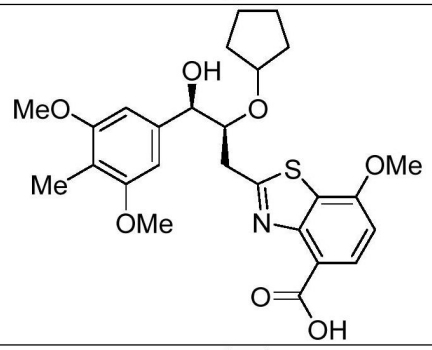
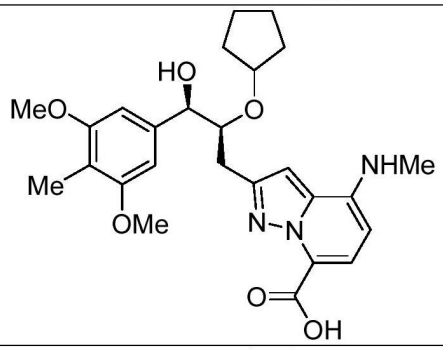
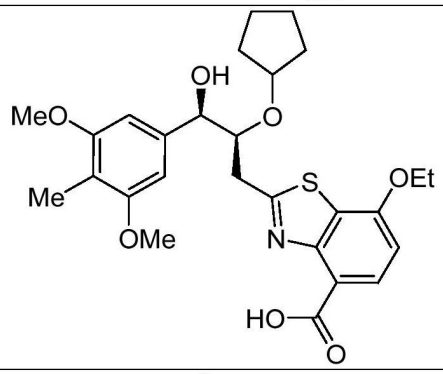
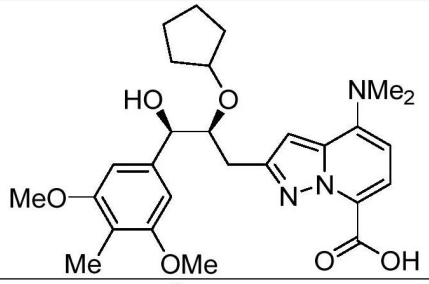
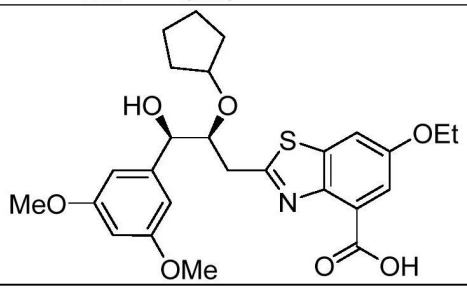
化合物

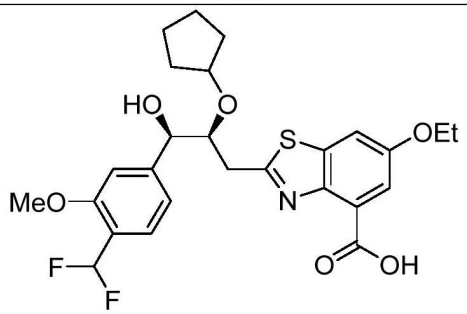
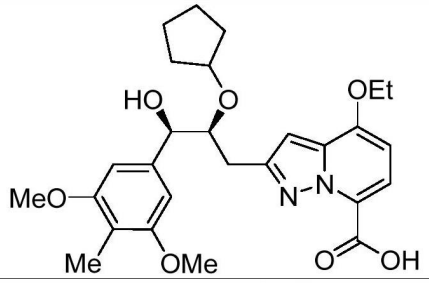
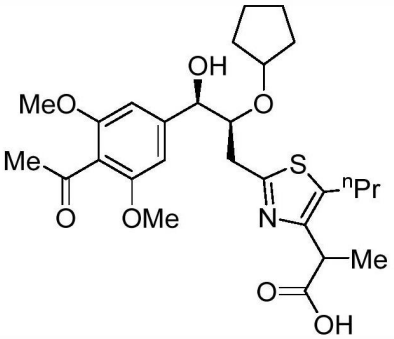
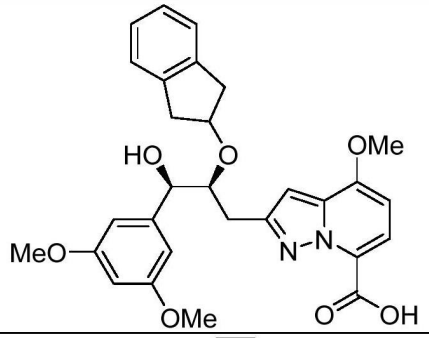
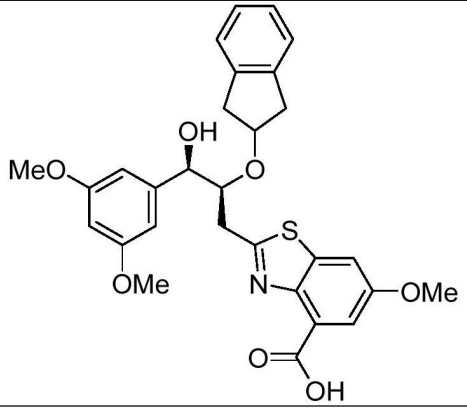
[0070] 本文提供了作为LPA拮抗剂的化合物。在一些实施方案中,提供了选自表1的化合物或其药学上可接受的盐或溶剂化物:

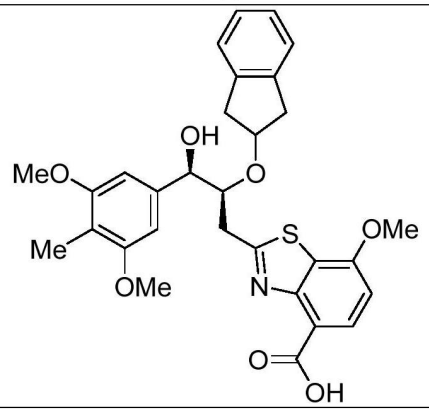
表1

化合物	结构
101	

化合物	结构
102	
103	
104	
105	
106	

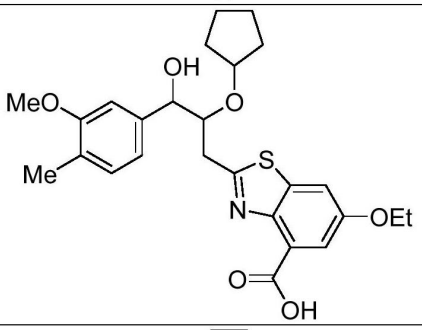
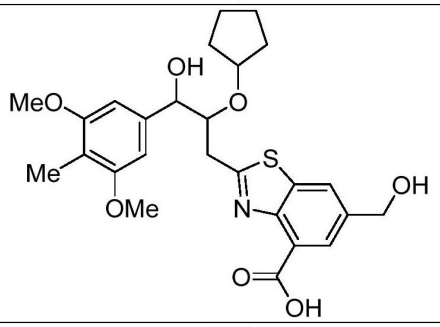
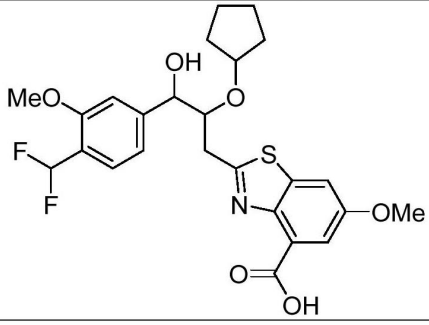
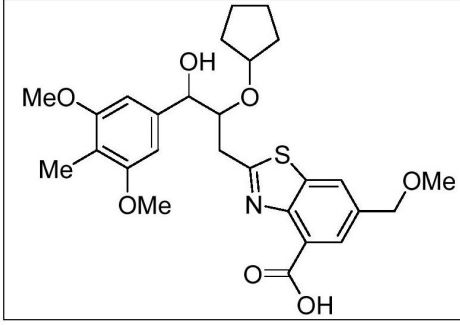
化合物	结构
107	
108	
109	
110	
111	

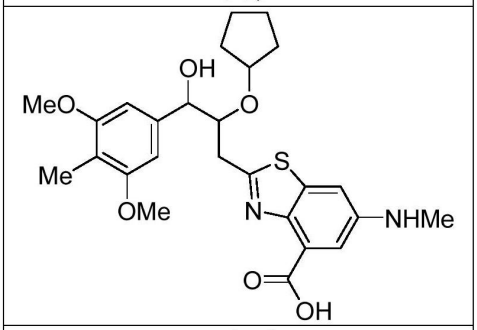
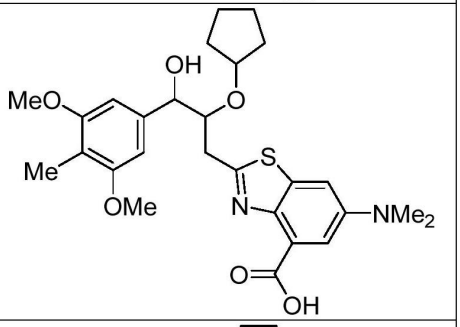
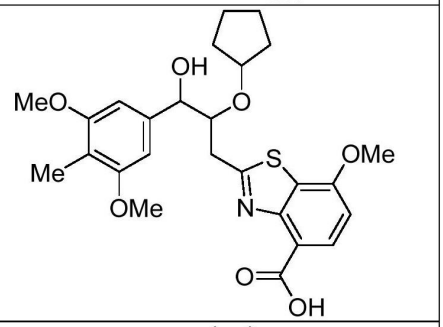
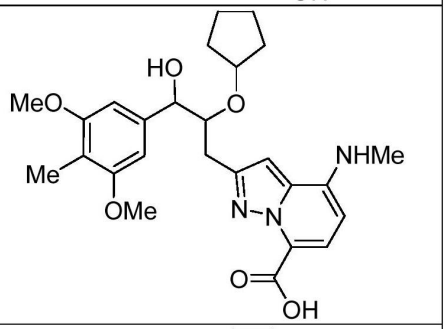
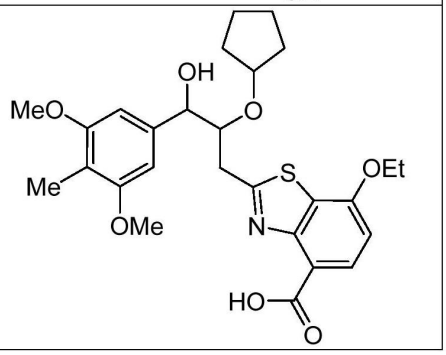
化合物	结构
112	
113	
114	
115	
116	

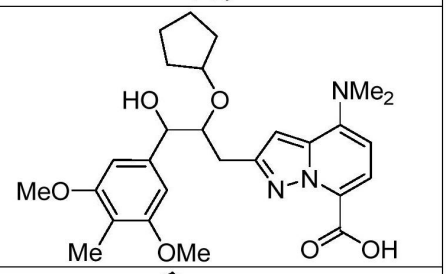
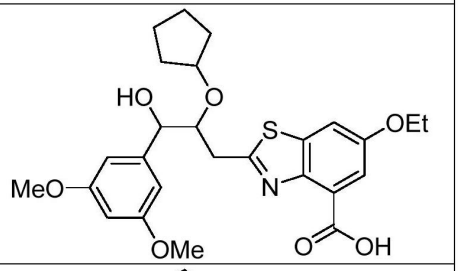
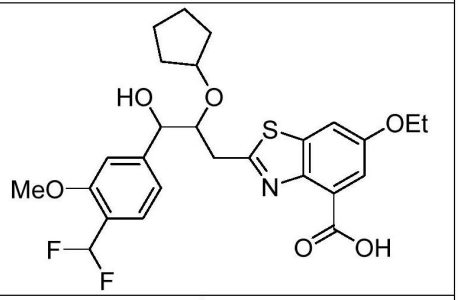
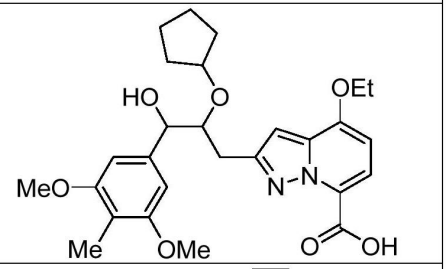
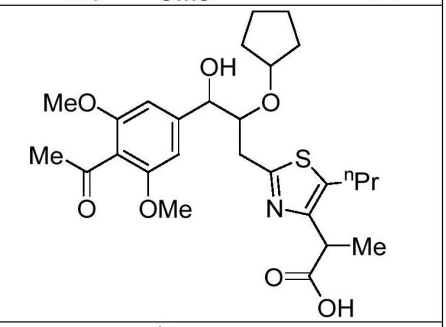
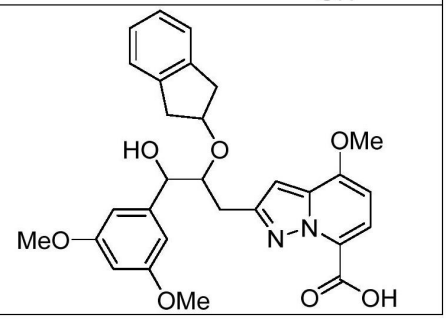
化合物	结构
117	

[0071] 本文提供的化合物涵盖所述化合物的立体化学形式(例如,旋光异构体,如对映异构体、非对映异构体)及其混合物,例如,对映异构体和/或非对映异构体的混合物,包括外消旋混合物以及单独对映异构体和/或非对映异构体的均等混合物或非均等混合物。本领域已知的方法可以用于确定绝对和/或相对构型,包括但不限于色谱法、光谱学、X射线晶体学等。本公开文本中考虑了所有立体化学形式。除非另有指示,否则当公开的化合物以结构命名或描述而没有指定立体化学并且具有一个或多个手性中心时,应理解为表示所述化合物的所有可能立体异构体,如表2中所描述的那些。在一些实施方案中,提供了选自表2的化合物或其药学上可接受的盐、溶剂化物、立体异构体或立体异构体的混合物。

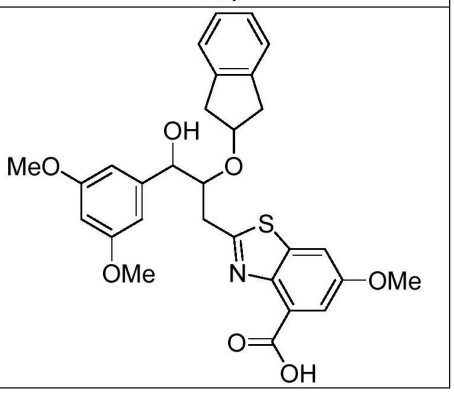
表2

结构	结构
	
	

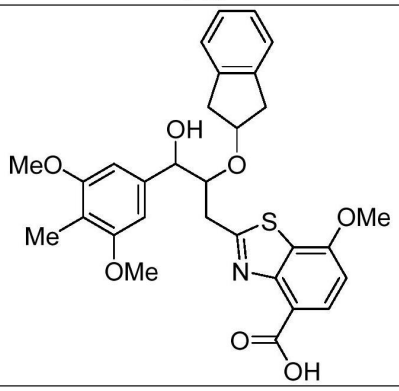
结构






结构







结构



结构



[0072] 本文公开的化合物包括其药学上可接受的盐。另外,本文公开的化合物还包括此类化合物的其他盐,所述盐不一定是药学上可接受的盐,并且所述盐可以用作制备和/或纯化本文公开的化合物和/或分离所述化合物的异构体或对映异构体的中间体。本文公开的化合物的药学上可接受的盐的非限制性例子包括三氟乙酸盐。

[0073] 进一步应理解,本文公开的化合物或其盐可以以溶剂化物的形式分离,并且相应地,任何此类溶剂化物包括在本公开文本的范围内。例如,本文公开的化合物及其盐可以以非溶剂化形式以及与药学上可接受的溶剂(如水、乙醇等)形成的溶剂化形式存在。

治疗方法与用途

[0074] 本文所述的方法可以在体内或离体应用于细胞群。“体内”意指在活个体内,如在动物体或人体内。在此背景中,本文所述的方法可以在个体中治疗性地使用。“离体”意指在活个体外。离体细胞群的例子包括体外细胞培养物和生物样品(包括从个体获得的流体或组织样品)。可以通过本领域熟知的方法获得此类样品。示例性生物流体样品包括血液、脑脊液、尿液和唾液。在此背景中,本文描述的化合物和组合物可用于多种目的,包括治疗和实验目的。例如,可以离体使用本文所述的化合物和组合物,以确定针对给定的适应证、细胞类型、个体和其他参数而言的本公开文本的化合物的施用的最佳时间表和/或配量。从这种用途中收集的信息可以用于实验目的,或者在临床中用于设定体内治疗方案。本文所述的化合物和组合物可适用的其他离体用途描述于下文或对本领域技术人员而言将变得清楚。可以进一步表征选定的化合物以检查在人类受试者或非人类受试者中的安全性或耐受剂量。可以使用本领域技术人员熟知的方法检查此类特性。

[0075] 如本文所提供的化合物或其药学上可接受的盐或溶剂化物,或此类化合物的药物组合物可用作一种或多种LPA受体的抑制剂。如本文中进一步描述的,拮抗LPA受体的化合物可以用于预防和/或治疗疾病,如包括以下的各种类疾病:例如纤维化(例如,肾脏纤维化、肺纤维化、肝纤维化、动脉纤维化、系统性硬化病)、泌尿系统疾病、癌相关疾病、增殖性疾病、炎症/免疫系统疾病、由分泌功能障碍引起的疾病、脑相关疾病和慢性疾病。

[0076] 在一些实施方案中,本公开文本提供了用于治疗患有疾病、障碍或病症的受试者(例如,人)的方法,在所述疾病、障碍或病症中一种或多种LPA受体(即,LPA相关疾病)的抑制有益于治疗所述疾病、障碍或病症的根本病理和/或症状和/或进展。在一些实施方案中,本文所提供的方法可以包括或进一步包括治疗与本文所提供的任一种或多种病症相关的一种或多种病症、共病或后遗症。

[0077] 本文提供了一种用于治疗LPA相关疾病的方法,所述方法包括向有需要的受试者

施用有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所公开的药物组合物。

[0078] 在一些实施方案中,LPA相关疾病包括但不限于治疗器官(例如,肝、肾、肺、心脏和皮肤)纤维化、肝疾病(急性肝炎、慢性肝炎、肝纤维化、肝硬化、门静脉高压、再生失效(regenerative failure)、非酒精性脂肪性肝炎(NASH)、肝功能减退、肝血流障碍等)、细胞增殖性疾病(例如,癌症,包括实体瘤、实体瘤转移、血管纤维瘤、骨髓瘤、多发性骨髓瘤、卡波西肉瘤(Kaposi's sarcoma)、白血病和慢性淋巴细胞白血病(CLL)和癌细胞的侵袭性转移)、炎性疾病(例如,银屑病、肾病和肺炎)、胃肠道疾病(例如,肠易激综合征(TBS)、炎性肠病(IBD)和胰腺分泌异常)、肾脏疾病、泌尿道相关疾病(例如,良性前列腺增生症或神经性膀胱疾病相关症状)、脊髓肿瘤、腰椎间盘突出症(hernia of intervertebral disk)、椎管狭窄症、源自糖尿病的症状、下泌尿道疾病(例如,下尿路梗阻)、下泌尿道的炎性疾病、排尿困难(dysuna)和尿频)、胰腺疾病、异常血管生成相关疾病(例如,动脉栓塞)、硬皮病、脑相关疾病(例如,脑梗死和脑出血)、神经性疼痛、外周神经病变、眼病(例如,年龄相关性黄斑病变(AMD)、糖尿病性视网膜病变、增生性玻璃体视网膜病变(PVR)、瘢痕性类天疱疮、和青光眼滤过术后瘢痕化(glaucoma filtration surgery scarring))。

[0079] 在一些实施方案中,本文提供了治疗或预防纤维化的方法,所述方法包括向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所公开的药物组合物。例如,方法可以包括治疗肾脏纤维化、肺纤维化、肝纤维化、动脉纤维化或系统性硬化病。在一些实施方案中,本文提供了治疗肺纤维化(例如,特发性肺纤维化(IPF))的方法,所述方法包括向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。

[0080] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗或预防受试者的纤维化。例如,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物可以用于治疗受试者的器官或组织的纤维化。在一些实施方案中,本文提供了一种用于预防受试者的纤维化病症的方法,所述方法包括向有风险患上一种或多种纤维化病症的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。例如,受试者可能暴露于已知会增加器官或组织的纤维化风险的一种或多种环境条件。在一些实施方案中,受试者暴露于已知会增加肺、肝或肾纤维化风险的一种或多种环境条件下。在一些实施方案中,受试者具有发生器官或组织的纤维化的遗传易感性。在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物施用于受试者,以预防或最小化损伤后的瘢痕化。例如,损伤可以包括手术。

[0081] 涉及纤维化的示例性疾病、障碍或病症包括但不限于:与纤维化相关的肺疾病(例如,特发性肺纤维化);医源性药物诱导的、职业/环境诱导的纤维化(农民肺);肉芽肿性疾病(结节病、过敏性肺炎);胶原血管疾病(硬皮病以及其他);肺泡蛋白沉积症;朗格汉斯细胞肉芽肿病;淋巴管平滑肌瘤病;遗传病(例如,海-普综合征(Hermansky-Pudlak Syndrome)、结节性硬化症、神经纤维瘤病、代谢蓄积障碍和家族性间质性肺疾病);继发于

全身性炎性疾病(如类风湿性关节炎、硬皮病、狼疮、隐源性致纤维化肺泡炎、辐射诱导的纤维化、慢性阻塞性肺疾病(COPD)、硬皮病、博来霉素诱导的肺纤维化、慢性哮喘、硅肺病、石棉诱导的肺或胸膜纤维化、急性肺损伤、急性呼吸窘迫综合征(ARDS)和急性呼吸窘迫(包括细菌性肺炎诱导的、创伤诱导的、病毒性肺炎诱导的、呼吸机诱导的、非肺脓毒症诱导的和误吸诱导的))的肺纤维化。与损伤/纤维化相关的慢性肾病、肾纤维化(肾脏纤维化)、继发于全身性炎性疾病(如狼疮和硬皮病、肾小管间质纤维化、肾小球肾炎、肾小球硬化、局灶节段性、糖尿病、肾小球肾炎、局灶节段性肾小球硬化、IgA肾病、高血压、同种异体移植和奥尔波特综合征(Alport syndrome))的血管球性肾炎;皮肤病学障碍、肠纤维化(例如,硬皮病和辐射诱导的肠纤维化);肝纤维化,例如肝硬化、酒精诱导的肝纤维化、非酒精性脂肪性肝炎(NASH)、非酒精性脂肪肝病(NAFLD)、毒性/药物诱导的肝纤维化(例如,血色素沉着病)、胆管损伤、原发性胆汁性肝硬化、感染或病毒诱导的纤维化(例如,慢性HCV感染)、炎性/免疫障碍和自身免疫性肝炎;头颈部纤维化,例如,角膜瘢痕(例如,LASIK(激光辅助原位角膜磨削术(laser-assisted in situ keratomileusis))、角膜移植和小梁切除术);增生性瘢痕、掌肌膜挛缩症(Duputren disease)、皮肤纤维化、皮肤硬皮病(cutaneous scleroderma)、瘢痕疙瘩(例如,烧伤诱导的或术后的);和其他纤维化疾病,例如结节病、硬皮病、脊髓损伤/纤维化、骨髓纤维化、血管再狭窄、动脉粥样硬化、动脉硬化、韦氏肉芽肿病、慢性淋巴细胞白血病、肿瘤转移、器官移植排斥(例如,闭塞性细支气管炎)、子宫内膜异位症、新生儿呼吸窘迫综合征和神经性疼痛、纤维肌痛、混合性结缔组织病和佩罗尼氏病(Peyronie's disease)。

[0082] 本文提供了一种改善受试者的肺功能的方法,所述方法包括向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。在一些实施方案中,受试者已被诊断为患有肺纤维化。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的特发性肺纤维化。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的寻常型间质性肺炎。

[0083] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的弥漫性实质间质性肺疾病,如医源性药物诱导的、职业/环境诱导的纤维化(农民肺)、肉芽肿性疾病(结节病、过敏性肺炎)、胶原血管病(硬皮病以及其他)、肺泡蛋白沉积症、朗格汉斯细胞肉芽肿病、淋巴管平滑肌瘤病、遗传病(例如,海-普综合征、结节性硬化症、神经纤维瘤病、代谢蓄积障碍和家族性间质性肺疾病)。

[0084] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的与慢性排斥相关的移植后纤维化,如肺移植后的闭塞性细支气管炎。

[0085] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的皮肤纤维化,如皮肤硬皮病、掌肌膜挛缩症和瘢痕疙瘩。

[0086] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接

受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的伴有或不伴有肝硬化的肝纤维化。例如,毒性/药物诱导的(血色素沉着病)、酒精性肝病、病毒性肝炎(乙型肝炎病毒、丙型肝炎病毒、HCV)、非酒精性肝病(NAFLD、NASH)以及代谢性和自身免疫性疾病。

[0087] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的肾脏纤维化(例如,肾小管间质纤维化和肾小球硬化)。

[0088] 如本文所提供的疾病、障碍或病症的进一步例子包括动脉粥样硬化、血栓形成、心脏病、血管炎、瘢痕组织形成、再狭窄、静脉炎、COPD(慢性阻塞性肺疾病)、肺动脉高压、肺纤维化、肺部炎症、肠粘连、膀胱纤维化和膀胱炎、鼻道纤维化、鼻窦炎、中性粒细胞介导的炎症和由成纤维细胞介导的纤维化。

[0089] 在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物与用于治疗纤维化的一种或多种其他药剂一起施用于患有器官或组织纤维化或具有患上器官或组织纤维化的倾向的受试者。在一些实施方案中,所述一种或多种药剂包括皮质类固醇、免疫抑制剂、B细胞拮抗剂和子宫珠蛋白。

[0090] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的皮肤病学障碍。此类皮肤病学障碍包括但不限于皮肤的增殖性或炎性障碍,如特应性皮炎、大疱性障碍、胶原性疾病(collagenoses)、银屑病、硬皮病、银屑病性病变(psoriatic lesion)、皮炎、接触性皮炎、湿疹、荨麻疹、酒渣鼻、伤口愈合、瘢痕、增生性瘢痕、瘢痕疙瘩、川崎病、酒渣鼻、舍格伦-拉松综合征(Sjogren-Larsso syndrome)或荨麻疹。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)用于治疗系统性硬化病。

[0091] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)用于治疗或预防受试者的炎症。例如,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)用于治疗或预防受试者的炎性/免疫障碍。

[0092] 炎性/免疫障碍的例子包括银屑病、类风湿性关节炎、血管炎、炎性肠病、皮炎、骨关节炎、哮喘、炎性肌肉疾病、过敏性鼻炎、阴道炎、间质性膀胱炎、硬皮病、湿疹、同种异体或异种移植(器官、骨髓、干细胞以及其他细胞和组织)移植物排斥、移植物抗宿主病、红斑狼疮、炎性疾病、I型糖尿病、肺纤维化、皮肌炎、舍格伦综合征(Sjogren's syndrome)、甲状腺炎(例如,桥本氏甲状腺炎和自身免疫性甲状腺炎)、重症肌无力、自身免疫性溶血性贫血、多发性硬化、囊性纤维化、慢性复发性肝炎、原发性胆汁性肝硬化、变应性结膜炎和特应性皮炎。

[0093] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的疼痛。在一些实施方案中,疼痛是急性疼痛或慢性疼痛。在一些实施方案中,疼痛是神经性疼痛。

[0094] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗纤维肌痛。纤维肌痛被认为起源于收缩肌(随意肌)中纤维瘢痕组织的形成。纤维化会束缚组织并且抑制血流,从而导致

疼痛。

[0095] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗癌症。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗恶性增殖性疾病和良性增殖性疾病。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于预防或减少肿瘤细胞的增殖、癌的侵袭和转移、胸膜间皮瘤(Yamada,Cancer Sci.,2008,99(8),1603-1610)或腹膜间皮瘤、癌性疼痛、骨转移癌(Boucharaba等人,J Clin.Invest.,2004,114(12),1714-1725;Boucharaba等人,Proc.Natl.Acad.Sci.,2006,103(25)9643-9648)。本文提供了一种治疗受试者的癌症的方法,所述方法包括向受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。在一些实施方案中,本文提供的方法进一步包括施用第二治疗剂,其中所述第二治疗剂是抗癌剂。

[0096] 如本文所用,术语“癌症”是指倾向于以不受控制的方式增殖并且在一些情况下转移(扩散)的细胞的异常生长。癌症的类型包括但不限于处于具有或不具有转移的任何疾病阶段的实体瘤(如膀胱、肠、脑、乳腺、子宫内膜、心脏、肾、肺、淋巴组织(淋巴瘤)、卵巢、胰腺或其他内分泌器官(甲状腺)、前列腺、皮肤(黑色素瘤或基底细胞癌)的那些)或血液肿瘤(如白血病)。

[0097] 癌症的另外的非限制性例子包括急性成淋巴细胞性白血病、急性髓系白血病、肾上腺皮质癌、肛门癌、阑尾癌、星形细胞瘤、非典型畸胎瘤样/横纹肌样瘤、基底细胞癌、胆管癌、膀胱癌、骨癌(骨肉瘤和恶性纤维组织细胞瘤)、脑干胶质瘤、脑肿瘤、脑和脊髓肿瘤、乳腺癌、支气管肿瘤、伯基特淋巴瘤、宫颈癌、慢性淋巴细胞白血病、慢性髓细胞性白血病、结肠癌、结直肠癌、颅咽管瘤、皮肤T细胞淋巴瘤、胚胎性肿瘤(embryonal tumor)、子宫内膜癌、成室管膜细胞瘤、室管膜瘤、食道癌、尤文氏肉瘤家族肿瘤(ewing sarcoma family of tumor)、眼癌、视网膜母细胞瘤、胆囊癌症、胃癌(gastric/stomach cancer)、胃肠道类癌肿瘤(gastrointestinal carcinoid tumor)、胃肠道间质瘤(GIST)、胃肠道间质细胞瘤、生殖细胞瘤、神经胶质瘤、毛细胞白血病、头颈癌、肝细胞(肝)癌、霍奇金淋巴瘤、下咽癌、眼内黑色素瘤、胰岛细胞瘤(内分泌胰腺)、卡波西肉瘤、肾癌、朗格汉斯细胞组织细胞增生症、喉癌、白血病、急性成淋巴细胞白血病,急性髓系白血病、慢性淋巴细胞白血病、慢性髓细胞性白血病、毛细胞白血病、肝癌、非小细胞肺癌、小细胞肺癌、伯基特淋巴瘤、皮肤T细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、淋巴瘤、华氏巨球蛋白血症(Waldenstrom macroglobulinemia)、髓母细胞瘤、髓上皮瘤、黑色素瘤、间皮瘤、口癌(mouth cancer)、慢性髓细胞性白血病、髓系白血病、多发性骨髓瘤、鼻咽癌、神经母细胞瘤、非霍奇金淋巴瘤、非小细胞肺癌、口腔癌(oral cancer)、口咽癌、骨肉瘤、骨恶性纤维组织细胞瘤、卵巢癌、上皮性卵巢癌、卵巢生殖细胞瘤、卵巢低度恶性潜能肿瘤(ovarian low malignant potential tumor)、胰腺癌、乳头瘤病、甲状旁腺癌、阴茎癌、咽癌、中分化松果体实质瘤、松果体母细胞瘤和幕上原始神经外胚层肿瘤、垂体瘤、浆细胞肿瘤/多发性骨髓瘤、胸膜肺胚细胞瘤、原发性中枢神经系统淋巴瘤、前列腺癌、直肠癌、肾细胞(肾)癌、视网膜母细胞瘤、横纹肌肉瘤、唾腺癌、肉瘤、尤文氏肉瘤家族肿瘤、肉瘤、卡波西肉瘤(kaposi)、塞扎里综合

征(Sezary syndrome)、皮肤癌、小细胞肺癌、小肠癌、软组织肉瘤、鳞状细胞癌、胃癌(stomach/gastric cancer)、幕上原始神经外胚层肿瘤、T细胞淋巴瘤、睾丸癌、喉癌、胸腺瘤和胸腺癌、甲状腺癌、尿道癌、子宫癌、子宫肉瘤、阴道癌、外阴癌、华氏巨球蛋白血症和肾母细胞瘤。

[0098] 在一些实施方案中,本文提供了一种治疗受试者的过敏性障碍的方法,所述方法包括施用治疗有效量的如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)可用于治疗受试者的呼吸系统疾病、障碍或病症。例如,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)可以治疗受试者的哮喘(例如,慢性哮喘)。

[0099] 如本文所用,术语“呼吸系统疾病”是指影响涉及呼吸的器官(如鼻、咽喉、喉、咽鼓管、气管、支气管、肺、相关肌肉(例如,膈和肋间的)和神经)的疾病。呼吸系统疾病的非限制性例子包括哮喘、成人型呼吸窘迫综合征和过敏性(外因性)哮喘、非过敏性(内因性)哮喘、急性重症哮喘、慢性哮喘、临床哮喘、夜间哮喘、过敏原诱导的哮喘、阿司匹林敏感性哮喘、运动诱发性哮喘、等二氧化碳过度通气(isocapnic hyperventilation)、儿童发作哮喘、成人发作哮喘、咳嗽变异性哮喘、职业性哮喘、类固醇抵抗型哮喘(steroid-resistant asthma)、季节性哮喘、季节性过敏性鼻炎、常年性过敏性鼻炎、慢性阻塞性肺疾病(包括慢性支气管炎或肺气肿、肺动脉高压、间质性肺纤维化和/或气道炎症和囊性纤维化、和缺氧)。

[0100] 如本文所用的术语“哮喘”是指特征在于与任何原因(内因性、外因性或两者兼有;过敏性的或非过敏性的)的气道狭窄相关的肺气流变化的任何肺部障碍。术语哮喘可以与一个或多个形容词一起使用以表明原因。

[0101] 本文进一步提供了用于治疗或预防受试者的慢性阻塞性肺疾病的方法,所述方法包括施用治疗有效量的如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。慢性阻塞性肺疾病的例子包括但不限于慢性支气管炎或肺气肿、肺动脉高压、间质性肺纤维化和/或气道炎症以及囊性纤维化。

[0102] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)用于治疗或预防受试者的神经系统障碍。如本文所用,术语“神经系统障碍”是指改变脑、脊髓或外周神经系统的结构或功能的病症,包括但不限于阿尔茨海默病、脑水肿、脑缺血、中风、多发性硬化、神经病变、帕金森病、钝挫伤或手术创伤后发现的病症(包括术后认知功能障碍和脊髓或脑干损伤);以及神经学方面的障碍(如退行性椎间盘疾病和坐骨神经痛)。

[0103] 在一些实施方案中,本文提供了用于治疗或预防受试者的CNS障碍的方法。CNS障碍的非限制性例子包括多发性硬化、帕金森病、阿尔茨海默病、中风、脑缺血、视网膜缺血、术后认知功能障碍、偏头痛、外周神经病变/神经性疼痛、脊髓损伤、脑水肿和头部损伤。

[0104] 本文还提供了治疗或预防受试者的心血管疾病的方法。如本文所用的术语“心血管疾病”是指影响心脏或血管或两者的疾病,包括但不限于:心律失常(arrhythmia)(心房性或心室性或两者);动脉粥样硬化及其后遗症;心绞痛;心脏节律异常(cardiac rhythm disturbance);心肌缺血;心肌梗塞;心脏或血管动脉瘤;血管炎、中风;肢体、器官或组织的

外周阻塞性动脉病;脑、心脏或其他器官或组织的缺血后再灌注损伤;内毒素休克、手术休克或创伤性休克;高血压、瓣膜性心脏病、心力衰竭、血压异常;休克;血管收缩(包括与偏头痛有关的血管收缩);血管异常、炎症、局限于单一器官或组织的功能不全。例如,本文提供了用于治疗或预防血管收缩、动脉粥样硬化及其后遗症心肌缺血、心肌梗死、主动脉瘤、血管炎和中风的方法,所述方法包括施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。

[0105] 在一些实施方案中,本文提供了用于减少心肌缺血和/或内毒素休克后的心脏再灌注损伤的方法,所述方法包括给向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。

[0106] 本文进一步提供了用于减少受试者的血管收缩的方法,所述方法包括施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。例如,本文提供了用于降低受试者血压或预防受试者血压升高的方法,所述方法包括施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。

[0107] 可以通过本领域已知的测定来证明测试化合物充当LGA受体抑制剂的能力。本文提供的作为LGA受体抑制剂的化合物和组合物的活性可以在体外、体内或细胞系中测定。

[0108] 例如,可以将过表达人LPA1的中国仓鼠卵巢细胞铺板在微孔板中的DMEM/F12培养基中过夜(15,000个细胞/孔)。过夜培养后,向细胞加载钙指示剂染料,在37℃下持续30分钟。然后在测定前将细胞平衡至室温持续30分钟。将溶解在DMSO中的测试化合物转移到多孔非结合表面板上并且用测定缓冲液(例如,具有钙/镁、20mM HEPES和0.1%无脂肪酸BSA的IX HBSS)稀释至最终浓度为0.5% DMSO。将稀释的化合物以0.08nM至5mM范围的最终浓度添加到细胞,并且然后在室温下孵育20min,此时以10nM的最终浓度添加LPA以刺激细胞。将化合物IC_{50}值定义为将由LPA单独诱导的钙通量抑制50%的测试化合物浓度。可以通过将数据拟合到4参数逻辑斯谛方程来确定IC_{50}值。

[0109] 在另一个例子中,在LPA激发之前2小时用本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)向CD-1雌性小鼠口服给药。然后用0.15mL的在0.1%BSA/PBS中的LPA(2pg/pL)经由尾静脉(IV)向小鼠给药。确切地在LPA激发后2分钟,通过断头术使小鼠安乐死并且收集躯干血。将这些样品集体离心并且将单独的75pL样品在-20℃下冷冻,直到进行组胺测定。血浆组胺分析可以通过标准EIA(酶免疫测定)方法进行。将血浆样品解冻并且在PBS中的0.1% BSA中以1:30稀释。如前所述的组胺分析的EIA方案可以用于本测定。

[0110] LPA具有作为生物效应分子的作用,并且具有广泛的生理作用(包括对血压、血小板活化和平滑肌收缩的影响),以及多种细胞效应,所述细胞效应包括细胞生长、细胞变圆、神经突回缩和肌动蛋白应力纤维形成和细胞迁移。这些作用主要是受体介导的。

[0111] 用LPA激活LPA受体(LPA_1、LPA_2、LPA_3、LPA_4、LPA_5、LPA_6)介导一系列下游信号传导级联。非限制性例子包括丝裂原活化蛋白激酶(MAPK)激活、腺苷酸环化酶(AC)抑制/激活、磷脂酶C(PLC)激活/Ca2+动员、花生四烯酸释放、Akt/PKB激活和小GTP酶、Rho、ROCK、Rae和Ras的激活。由LPA受体激活影响的另外的途径包括例如环腺苷一磷酸(cAMP)、细胞分裂周期42/GTP结合蛋白(Cdc42)、原癌基因丝氨酸/苏氨酸蛋白激酶Raf(c-RAF)、原癌基因酪氨酸

蛋白激酶Src(c-src)、细胞外信号调节激酶(ERK)、粘附斑激酶(FAK)、鸟嘌呤核苷酸交换因子(GEF)、糖原合成酶激酶3b(GSK3b)、c-jun氨基末端激酶(JNK)、MEK、肌球蛋白轻链II(MLC II)、核因子kB(NF-kB)、N-甲基-D-天冬氨酸(NMDA)受体激活、磷脂酰肌醇3激酶(PBK)、蛋白激酶A(PKA)、蛋白激酶C(PKC)、ms相关C3肉毒菌毒素底物1(RAC1)。几乎所有哺乳动物的细胞、组织和器官都共同表达几种LPA受体亚型,这表明LPA受体以合作的方式进行信号传导。LPA1、LPA2和LPA3共享高氨基酸序列相似性。

[0112] LPA_1(以前称为VZG-1/EDG-2/mrec1.3)与三类G蛋白($G_{i/o}$、G_q和$G_{12/13}$)偶联。通过激活这些G蛋白,LPA通过LPA_1诱导一系列细胞反应,包括例如细胞增殖、血清反应元件(SRE)激活、丝裂原活化蛋白激酶(MAPK)激活、腺苷酸环化酶(AC)抑制、磷脂酶C(PLC)激活、Ca^{2+}动员、Akt激活和Rho激活。

[0113] 在小鼠的睾丸、脑、心脏、肺、小肠、胃、脾脏、胸腺和骨骼肌中观察到LPA_1的表达。类似地,LPA_1在如脑、心脏、肺、胎盘、结肠、小肠、前列腺、睾丸、卵巢、胰腺、脾脏、肾、骨骼肌和胸腺的人组织中表达。

[0114] LPA_2(EDG-4)还与三类G蛋白($G_{i/o}$、G_q和$G_{12/13}$)偶联以介导LPA诱导的细胞信号传导。在成年小鼠的睾丸、肾、肺、胸腺、脾脏和胃以及人的睾丸、胰腺、前列腺、胸腺、脾脏和外周血白细胞中观察到LPA_2的表达。LPA_2的表达在各种癌细胞系中上调,并且已经观察到几种在3'-非翻译区具有突变的人LPA_2转录变体。

[0115] LPA_3可以介导多效性LPA诱导的信号传导,包括PLC激活、Ca^{2+}动员、AC抑制/激活和MAPK激活。LPA3在神经母细胞瘤细胞中的过表达导致神经突伸长。在成年小鼠睾丸、肾、肺、小肠、心脏、胸腺和脑中观察到LPA_3的表达。在人类中,它发现于心脏、胰腺、前列腺、睾丸、肺、卵巢和脑(皮质额叶、海马体和杏仁体)。

[0116] 与LPA_1、LPA_2和LPA_3相比,LPA_4($p2y_9$/GPR23)具有不同的序列,与血小板活化因子(PAF)受体的相似性更近。LPA_4介导LPA诱导的Ca^{2+}动员和cAMP积累,以及与G蛋白Gs的功能偶联以激活AC,以及与其他G蛋白的偶联。LPA_4基因在卵巢、胰腺、胸腺、肾和骨骼肌中表达。

[0117] LPA_5(GPR92)是GPCR的嘌呤簇(purinocluster)的成员并且结构上与LPA_4关系最密切。LPA_5在人的心脏、胎盘、脾脏、脑、肺和肠道中表达。LPA在胃肠道的CD8+淋巴细胞隔室也显示出非常高的表达。

[0118] LPA_6(p2y5)是GPCR的嘌呤簇(purinocluster)的成员并且结构上与LPA_4关系最密切。LPA_6是一种与G12/13-Rho信号传导通路偶联的LPA受体并且在人类毛囊的内根鞘中表达。

[0119] 通过本公开文本的方法具体提供了对任何前述反应标准的改进。

组合疗法

[0120] 在一个实施方案中,本文公开的化合物可以与用于和/或开发用于治疗疾病、障碍或病症的一种或多种另外的治疗剂组合使用,其中一种或多种LPA受体的抑制对于治疗所述疾病、障碍或病症(即,LPA相关疾病)的潜在病理和/或症状和/或进展有益。

[0121] 如本文所提供的化合物或其药学上可接受的盐或溶剂化物,或此类化合物的药物组合物可用作一种或多种LPA受体的抑制剂。如本文中进一步描述的,拮抗LPA受体的化合物可以用于预防和/或治疗疾病,如包括以下的各种类疾病:例如纤维化(例如,肾脏纤维化、肺纤维化、肝纤维化、动脉纤维化、系统性硬化病)、泌尿系统疾病、癌相关疾病、增殖性

疾病、炎症/免疫系统疾病、由分泌功能障碍引起的疾病、脑相关疾病和慢性疾病。

[0122] 在一些实施方案中,本公开文本提供了用于治疗患有疾病、障碍或病症的受试者(例如,人)的方法,在所述疾病、障碍或病症中一种或多种LPA受体(即,LPA相关疾病)的抑制有益于治疗所述疾病、障碍或病症的根本病理和/或症状和/或进展。在一些实施方案中,本文所提供的方法可以包括或进一步包括治疗与本文所提供的任一种或多种病症相关的一种或多种病症、共病或后遗症。

[0123] 本文提供了一种用于治疗LPA相关疾病的方法,所述方法包括向有需要的受试者施用有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所公开的药物组合物。

[0124] 在一些实施方案中,LPA相关疾病包括但不限于治疗器官(例如,肝、肾、肺、心脏和皮肤)纤维化、肝疾病(急性肝炎、慢性肝炎、肝纤维化、肝硬化、门静脉高压、再生失效(regenerative failure)、非酒精性脂肪性肝炎(NASH)、肝功能减退、肝血流障碍等)、细胞增殖性疾病(例如,癌症,包括实体瘤、实体瘤转移、血管纤维瘤、骨髓瘤、多发性骨髓瘤、卡波西肉瘤(Kaposi's sarcoma)、白血病和慢性淋巴细胞白血病(CLL)和癌细胞的侵袭性转移)、炎性疾病(例如,银屑病、肾病和肺炎)、胃肠道疾病(例如,肠易激综合征(TBS)、炎性肠病(IBD)和胰腺分泌异常)、肾脏疾病、泌尿道相关疾病(例如,良性前列腺增生症或神经性膀胱疾病相关症状)、脊髓肿瘤、腰椎间盘突出症(hernia of intervertebral disk)、椎管狭窄症、源自糖尿病的症状、下泌尿道疾病(例如,下尿路梗阻)、下泌尿道的炎性疾病、排尿困难(dysuna)和尿频)、胰腺疾病、异常血管生成相关疾病(例如,动脉栓塞)、硬皮病、脑相关疾病(例如,脑梗死和脑出血)、神经性疼痛、外周神经病变、眼病(例如,年龄相关性黄斑病变(AMD)、糖尿病性视网膜病变、增生性玻璃体视网膜病变(PVR)、瘢痕性类天疱疮、和青光眼滤过术后瘢痕化(glaucoma filtration surgery scarring))。

[0125] 在一些实施方案中,本文提供了治疗或预防纤维化的方法,所述方法包括向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所公开的药物组合物。例如,方法可以包括治疗肾脏纤维化、肺纤维化、肝纤维化、动脉纤维化或系统性硬化病。在一些实施方案中,本文提供了治疗肺纤维化(例如,特发性肺纤维化(IPF))的方法,所述方法包括向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。

[0126] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗或预防受试者的纤维化。例如,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物可以用于治疗受试者的器官或组织的纤维化。在一些实施方案中,本文提供了一种用于预防受试者的纤维化病症的方法,所述方法包括向有风险患上一种或多种纤维化病症的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。例如,受试者可能暴露于已知会增加器官或组织的纤维化风险的一种或多种环境条件。在一些实施方案中,受试者暴露于已知会增加肺、肝或肾纤维化风险的一种或多种环境条件下。在一些实施方案中,受试者具有发生器官或组织的纤维化的遗传易感性。在一些实施方案中,将本文公开的化合

物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物施用于受试者,以预防或最小化损伤后的瘢痕化。例如,损伤可以包括手术。

[0127] 涉及纤维化的示例性疾病、障碍或病症包括但不限于:与纤维化相关的肺疾病(例如,特发性肺纤维化);医源性药物诱导的、职业/环境诱导的纤维化(农民肺);肉芽肿性疾病(结节病、过敏性肺炎);胶原血管疾病(硬皮病以及其他);肺泡蛋白沉积症;朗格汉斯细胞肉芽肿病;淋巴管平滑肌瘤病;遗传病(例如,海-普综合征(Hermansky-Pudlak Syndrome)、结节性硬化症、神经纤维瘤病、代谢蓄积障碍和家族性间质性肺疾病);继发于全身性炎性疾病(如类风湿性关节炎、硬皮病、狼疮、隐源性致纤维化肺泡炎、辐射诱导的纤维化、慢性阻塞性肺疾病(COPD)、硬皮病、博来霉素诱导的肺纤维化、慢性哮喘、硅肺病、石棉诱导的肺或胸膜纤维化、急性肺损伤、急性呼吸窘迫综合征(ARDS)和急性呼吸窘迫(包括细菌性肺炎诱导的、创伤诱导的、病毒性肺炎诱导的、呼吸机诱导的、非肺脓毒症诱导的和误吸诱导的))的肺纤维化。与损伤/纤维化相关的慢性肾病、肾纤维化(肾脏纤维化)、继发于全身性炎性疾病(如狼疮和硬皮病、肾小管间质纤维化、肾小球肾炎、肾小球硬化、局灶节段性、糖尿病、肾小球肾炎、局灶节段性肾小球硬化、IgA肾病、高血压、同种异体移植和奥尔波特综合征(Alport syndrome))的血管球性肾炎;皮肤病学障碍、肠纤维化(例如,硬皮病和辐射诱导的肠纤维化);肝纤维化,例如肝硬化、酒精诱导的肝纤维化、非酒精性脂肪性肝炎(NASH)、非酒精性脂肪肝病(NAFLD)、毒性/药物诱导的肝纤维化(例如,血色素沉着病)、胆管损伤、原发性胆汁性肝硬化、感染或病毒诱导的纤维化(例如,慢性HCV感染)、炎性/免疫障碍和自身免疫性肝炎;头颈部纤维化,例如,角膜瘢痕(例如,LASIK(激光辅助原位角膜磨削术(laser-assisted in situ keratomileusis))、角膜移植和小梁切除术);增生性瘢痕、掌肌膜挛缩症(Duputren disease)、皮肤纤维化、皮肤硬皮病(cutaneous sceroderma)、瘢痕疙瘩(例如,烧伤诱导的或术后的);和其他纤维化疾病,例如结节病、硬皮病、脊髓损伤/纤维化、骨髓纤维化、血管再狭窄、动脉粥样硬化、动脉硬化、韦氏肉芽肿病、慢性淋巴细胞白血病、肿瘤转移、器官移植排斥(例如,闭塞性细支气管炎)、子宫内膜异位症、新生儿呼吸窘迫综合征和神经性疼痛、纤维肌痛、混合性结缔组织病和佩罗尼氏病(Peyronie's disease)。

[0128] 本文提供了一种改善受试者的肺功能的方法,所述方法包括向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。在一些实施方案中,受试者已被诊断为患有肺纤维化。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的特发性肺纤维化。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的寻常型间质性肺炎。

[0129] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的弥漫性实质间质性肺疾病,如医源性药物诱导的、职业/环境诱导的纤维化(农民肺)、肉芽肿性疾病(结节病、过敏性肺炎)、胶原血管病(硬皮病以及其他)、肺泡蛋白沉积症、朗格汉斯细胞肉芽肿病、淋巴管平滑肌瘤病、遗传病(例如,海-普综合征、结节性硬化症、神经纤维瘤病、代谢蓄积障碍和家族性间质性肺疾病)。

[0130] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的与慢性排斥相关的移植后纤维化,如肺移植后的闭塞性细支气管炎。

[0131] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的皮肤纤维化,如皮肤硬皮病、掌肌膜挛缩症和瘢痕疙瘩。

[0132] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的伴有或不伴有肝硬化的肝纤维化。例如,毒性/药物诱导的(血色素沉着病)、酒精性肝病、病毒性肝炎(乙型肝炎病毒、丙型肝炎病毒、HCV)、非酒精性肝病(NAFLD、NASH)以及代谢性和自身免疫性疾病。

[0133] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的肾脏纤维化(例如,肾小管间质纤维化和肾小球硬化)。

[0134] 如本文所提供的疾病、障碍或病症的进一步例子包括动脉粥样硬化、血栓形成、心脏病、血管炎、瘢痕组织形成、再狭窄、静脉炎、COPD(慢性阻塞性肺疾病)、肺动脉高压、肺纤维化、肺部炎症、肠粘连、膀胱纤维化和膀胱炎、鼻道纤维化、鼻窦炎、中性粒细胞介导的炎症和由成纤维细胞介导的纤维化。

[0135] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物可用于治疗COVID-19的一种或多种症状。

[0136] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物可用于治疗慢性阻塞性肺疾病(COPD)。

[0137] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物可用于治疗神经炎症。

[0138] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物可用于治疗多发性硬化。

[0139] 在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物与用于治疗纤维化的一种或多种其他药剂一起施用于患有器官或组织纤维化或具有患上器官或组织纤维化的倾向的受试者。在一些实施方案中,所述一种或多种药剂包括皮质类固醇、免疫抑制剂、B细胞拮抗剂和子宫珠蛋白。

[0140] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的皮肤病学障碍。此类皮肤病学障碍包括但不限于皮肤的增殖性或炎性障碍,如特应性皮炎、大疱性障碍、胶原性疾病(collagenoses)、银屑病、硬皮病、银屑病性病变(psoriatic lesion)、皮炎、接触性皮炎、湿疹、荨麻疹、酒渣鼻、伤口愈合、瘢痕、增生性瘢痕、瘢痕疙瘩、川崎病、酒渣鼻、舍格伦-拉松综合征(Sjogren-Larsso syndrome)或荨麻疹。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)用于治疗系统性硬化病。

[0141] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接

受的盐或溶剂化物)用于治疗或预防受试者的炎症。例如,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)用于治疗或预防受试者的炎性/免疫障碍。

[0142] 炎性/免疫障碍的例子包括银屑病、类风湿性关节炎、血管炎、炎性肠病、皮炎、骨关节炎、哮喘、炎性肌肉疾病、过敏性鼻炎、阴道炎、间质性膀胱炎、硬皮病、湿疹、同种异体或异种移植(器官、骨髓、干细胞以及其他细胞和组织)移植物排斥、移植物抗宿主病、红斑狼疮、炎性疾病、I型糖尿病、肺纤维化、皮肌炎、舍格伦综合征(Sjogren's syndrome)、甲状腺炎(例如,桥本氏甲状腺炎和自身免疫性甲状腺炎)、重症肌无力、自身免疫性溶血性贫血、多发性硬化、囊性纤维化、慢性复发性肝炎、原发性胆汁性肝硬化、变应性结膜炎和特应性皮炎。

[0143] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗受试者的疼痛。在一些实施方案中,疼痛是急性疼痛或慢性疼痛。在一些实施方案中,疼痛是神经性疼痛。

[0144] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗纤维肌痛。纤维肌痛被认为起源于收缩肌(随意肌)中纤维瘢痕组织的形成。纤维化会束缚组织并且抑制血流,从而导致疼痛。

[0145] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗癌症。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于治疗恶性增殖性疾病和良性增殖性疾病。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物用于预防或减少肿瘤细胞的增殖、癌的侵袭和转移、胸膜间皮瘤(Yamada,Cancer Sci.,2008,99(8),1603-1610)或腹膜间皮瘤、癌性疼痛、骨转移癌(Boucharaba等人,J Clin.Invest.,2004,114(12),1714-1725;Boucharaba等人,Proc.Natl.Acad.Sci.,2006,103(25)9643-9648)。本文提供了一种治疗受试者的癌症的方法,所述方法包括向受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物。在一些实施方案中,本文提供的方法进一步包括施用第二治疗剂,其中所述第二治疗剂是抗癌剂。

[0146] 如本文所用,术语"癌症"是指倾向于以不受控制的方式增殖并且在一些情况下转移(扩散)的细胞的异常生长。癌症的类型包括但不限于处于具有或不具有转移的任何疾病阶段的实体瘤(如膀胱、肠、脑、乳腺、子宫内膜、心脏、肾、肺、淋巴组织(淋巴瘤)、卵巢、胰腺或其他内分泌器官(甲状腺)、前列腺、皮肤(黑色素瘤或基底细胞癌)的那些)或血液肿瘤(如白血病)。

[0147] 癌症的另外的非限制性例子包括急性成淋巴细胞性白血病、急性髓系白血病、肾上腺皮质癌、肛门癌、阑尾癌、星形细胞瘤、非典型畸胎瘤样/横纹肌样瘤、基底细胞癌、胆管癌、膀胱癌、骨癌(骨肉瘤和恶性纤维组织细胞瘤)、脑干胶质瘤、脑肿瘤、脑和脊髓肿瘤、乳腺癌、支气管肿瘤、伯基特淋巴瘤、宫颈癌、慢性淋巴细胞白血病、慢性髓细胞性白血病、结肠癌、结直肠癌、颅咽管瘤、皮肤T细胞淋巴瘤、胚胎性肿瘤(embryonal tumor)、子宫内膜

癌、成室管膜细胞瘤、室管膜瘤、食道癌、尤文氏肉瘤家族肿瘤(ewing sarcoma family of tumor)、眼癌、视网膜母细胞瘤、胆囊癌症、胃癌(gastric/stomach cancer)、胃肠道类癌肿瘤(gastrointestinal carcinoid tumor)、胃肠道间质瘤(GIST)、胃肠道间质细胞瘤、生殖细胞瘤、神经胶质瘤、毛细胞白血病、头颈癌、肝细胞(肝)癌、霍奇金淋巴瘤、下咽癌、眼内黑色素瘤、胰岛细胞瘤(内分泌胰腺)、卡波西肉瘤、肾癌、朗格汉斯细胞组织细胞增生症、喉癌、白血病、急性成淋巴细胞白血病,急性髓系白血病、慢性淋巴细胞白血病、慢性髓细胞性白血病、毛细胞白血病、肝癌、非小细胞肺癌、小细胞肺癌、伯基特淋巴瘤、皮肤T细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、淋巴瘤、华氏巨球蛋白血症(Waldenstrom macroglobulinemia)、髓母细胞瘤、髓上皮瘤、黑色素瘤、间皮瘤、口癌(mouth cancer)、慢性髓细胞性白血病、髓系白血病、多发性骨髓瘤、鼻咽癌、神经母细胞瘤、非霍奇金淋巴瘤、非小细胞肺癌、口腔癌(oral cancer)、口咽癌、骨肉瘤、骨恶性纤维组织细胞瘤、卵巢癌、上皮性卵巢癌、卵巢生殖细胞瘤、卵巢低度恶性潜能肿瘤(ovarian low malignant potential tumor)、胰腺癌、乳头瘤病、甲状旁腺癌、阴茎癌、咽癌、中分化松果体实质瘤、松果体母细胞瘤和幕上原始神经外胚层肿瘤、垂体瘤、浆细胞肿瘤/多发性骨髓瘤、胸膜肺胚细胞瘤、原发性中枢神经系统淋巴瘤、前列腺癌、直肠癌、肾细胞(肾)癌、视网膜母细胞瘤、横纹肌肉瘤、唾腺癌、肉瘤、尤文氏肉瘤家族肿瘤、肉瘤、卡波西肉瘤(kaposi)、塞扎里综合征(Sezary syndrome)、皮肤癌、小细胞肺癌、小肠癌、软组织肉瘤、鳞状细胞癌、胃癌(stomach/gastric cancer)、幕上原始神经外胚层肿瘤、T细胞淋巴瘤、睾丸癌、喉癌、胸腺瘤和胸腺癌、甲状腺癌、尿道癌、子宫癌、子宫肉瘤、阴道癌、外阴癌、华氏巨球蛋白血症和肾母细胞瘤。

[0148] 在一些实施方案中,本文提供了一种治疗受试者的过敏性障碍的方法,所述方法包括施用治疗有效量的如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)可用于治疗受试者的呼吸系统疾病、障碍或病症。例如,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)可以治疗受试者的哮喘(例如,慢性哮喘)。

[0149] 如本文所用,术语“呼吸系统疾病”是指影响涉及呼吸的器官(如鼻、咽喉、喉、咽鼓管、气管、支气管、肺、相关肌肉(例如,膈和肋间的)和神经)的疾病。呼吸系统疾病的非限制性例子包括哮喘、成人型呼吸窘迫综合征和过敏性(外因性)哮喘、非过敏性(内因性)哮喘、急性重症哮喘、慢性哮喘、临床哮喘、夜间哮喘、过敏原诱导的哮喘、阿司匹林敏感性哮喘、运动诱发性哮喘、等二氧化碳过度通气(isocapnic hyperventilation)、儿童发作哮喘、成人发作哮喘、咳嗽变异性哮喘、职业性哮喘、类固醇抵抗型哮喘(steroid-resistant asthma)、季节性哮喘、季节性过敏性鼻炎、常年性过敏性鼻炎、慢性阻塞性肺疾病(包括慢性支气管炎或肺气肿、肺动脉高压、间质性肺纤维化和/或气道炎症和囊性纤维化、和缺氧)。

[0150] 如本文所用的术语“哮喘”是指特征在于与任何原因(内因性、外因性或两者兼有;过敏性的或非过敏性的)的气道狭窄相关的肺气流变化的任何肺部障碍。术语哮喘可以与一个或多个形容词一起使用以表明原因。

[0151] 本文进一步提供了用于治疗或预防受试者的慢性阻塞性肺疾病的方法,所述方法

包括施用治疗有效量的如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。慢性阻塞性肺疾病的例子包括但不限于慢性支气管炎或肺气肿、肺动脉高压、间质性肺纤维化和/或气道炎症以及囊性纤维化。

[0152] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)用于治疗或预防受试者的神经系统障碍。如本文所用,术语"神经系统障碍"是指改变脑、脊髓或外周神经系统的结构或功能的病症,包括但不限于阿尔茨海默病、脑水肿、脑缺血、中风、多发性硬化、神经病变、帕金森病、钝挫伤或手术创伤后发现的病症(包括术后认知功能障碍和脊髓或脑干损伤);以及神经学方面的障碍(如退行性椎间盘疾病和坐骨神经痛)。

[0153] 在一些实施方案中,本文提供了用于治疗或预防受试者的CNS障碍的方法。CNS障碍的非限制性例子包括多发性硬化、帕金森病、阿尔茨海默病、中风、脑缺血、视网膜缺血、术后认知功能障碍、偏头痛、外周神经病变/神经性疼痛、脊髓损伤、脑水肿和头部损伤。

[0154] 本文还提供了治疗或预防受试者的心血管疾病的方法。如本文所用的术语"心血管疾病"是指影响心脏或血管或两者的疾病,包括但不限于:心律失常(arrhythmia)(心房性或心室性或两者);动脉粥样硬化及其后遗症;心绞痛;心脏节律异常(cardiac rhythm disturbance);心肌缺血;心肌梗塞;心脏或血管动脉瘤;血管炎、中风;肢体、器官或组织的外周阻塞性动脉病;脑、心脏或其他器官或组织的缺血后再灌注损伤;内毒素休克、手术休克或创伤性休克;高血压、瓣膜性心脏病、心力衰竭、血压异常;休克;血管收缩(包括与偏头痛有关的血管收缩);血管异常、炎症、局限于单一器官或组织的功能不全。例如,本文提供了用于治疗或预防血管收缩、动脉粥样硬化及其后遗症心肌缺血、心肌梗死、主动脉瘤、血管炎和中风的方法,所述方法包括施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。

[0155] 在一些实施方案中,本文提供了用于减少心肌缺血和/或内毒素休克后的心脏再灌注损伤的方法,所述方法包括给向有需要的受试者施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。

[0156] 本文进一步提供了用于减少受试者的血管收缩的方法,所述方法包括施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。例如,本文提供了用于降低受试者血压或预防受试者血压升高的方法,所述方法包括施用治疗有效量的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)。

药物组合物和施用模式

[0157] 本文提供的化合物通常以药物组合物的形式施用。

[0158] 当用作药物时,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)(包括其药学上可以接受的盐或溶剂化物)可以以药物组合物的形式施用。这些组合物能以药学领域中所熟知的方式制备,并且可以通过各种途径施用,这取决于是希望局部治疗还是希望全身治疗以及待治疗的区域。施用可以是外用(包括透皮、表皮、眼部和粘膜,包括鼻内、阴道和直肠递送)、肺部(例如,通过吸入或吹入散剂或气雾剂,包括通过雾化器;气管内或鼻内)、口服或肠胃外。口服施用可以包括配制用于每天一次或每天两次(BID)施用的剂型。肠胃外施用包括静脉内、动脉内、皮下、腹膜内肌内或注射或输注;或

颅内,例如鞘内或心室内施用。肠胃外施用可以呈单次推注剂量的形式或者可以例如通过连续灌注泵。用于外用施用的药物组合物和配制品可以包括透皮贴剂、软膏、洗剂、乳膏、凝胶、滴剂、栓剂、喷雾剂、液体以及散剂。常规的药物载体、水性基质、粉末基质或油性基质、增稠剂等可以是需要的或希望的。

[0159] 本文还提供了药物组合物,所述药物组合物含有作为活性成分的本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)与一种或多种药学上可接受的赋形剂(载体)的组合。例如,使用本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)制备的药物组合物。在一些实施方案中,组合物适用于局部施用。在制造本文提供的组合物中,典型地将活性成分与赋形剂混合,用赋形剂稀释或封装在这样的载体内,所述载体呈例如胶囊、小药囊(sachet)、纸或其他容器的形式。当赋形剂用作稀释剂时,它可以是固体、半固体或液体材料,所述材料充当活性成分的媒介物、载体或介质。因此,组合物可以处于片剂、丸剂、散剂、锭剂、小袋、扁囊剂、酏剂、混悬剂、乳剂、溶液、糖浆、气雾剂(作为固体或在液体介质中)、软膏(含有例如以活性化合物的重量计至多10%)、软和硬明胶胶囊、栓剂、无菌注射溶液、和无菌包装散剂的形式。在一些实施方案中,组合物被配制用于口服施用。在一些实施方案中,组合物是固体口服配制品。在一些实施方案中,组合物被配制为片剂或胶囊。

[0160] 本文进一步提供了含有本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)与药学上可接受的赋形剂的药物组合物。含有本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)作为活性成分的药物组合物可以通过根据常规药物混配技术将本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2中的化合物或其药学上可以接受的盐或溶剂化物)与药物载体紧密混合来制备。载体可以采用许多种形式,取决于所希望的施用途径(例如,口服、肠胃外)。在一些实施方案中,组合物是固体口服组合物。

[0161] 合适的药学上可接受的载体是本领域熟知的。这些药学上可接受的载体中的一些的描述可以在由the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain出版的The Handbook of Pharmaceutical Excipients中找到。

[0162] 配制药物组合物的方法已描述在大量出版物中,如Pharmaceutical Dosage Forms:Tablets,第二版,增订版,第1-3卷,由Lieberman等人编辑;Pharmaceutical Dosage Forms:Parenteral Medications,第1-2卷,由Avis等人编辑;和Pharmaceutical Dosage Forms:Disperse Systems,第1-2卷,由Lieberman等人编辑;由Marcel Dekker,Inc.出版。

[0163] 药学上可接受的赋形剂包括但不限于离子交换剂;氧化铝;硬脂酸铝;卵磷脂;自乳化药物递送系统(SEDDS),如d-α-生育酚聚乙二醇1000琥珀酸酯;以药物剂型使用的表面活性剂,如Tween、泊洛沙姆(poloxamer)或其他类似聚合物递送基体;血清蛋白,如人血清白蛋白;缓冲物质,如磷酸盐、tris、甘氨酸、山梨酸、山梨酸钾;饱和植物脂肪酸的偏甘油酯混合物;水、盐或电解质,如硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠;锌盐;胶态二氧化硅;三硅酸镁;聚乙烯吡咯烷酮;基于纤维素的物质;聚乙二醇;羧甲基纤维素钠;聚丙烯

酸酯;蜡;聚乙烯-聚氧化丙烯嵌段共聚物;以及羊毛脂。环糊精(如α-环糊精、β-环糊精和γ-环糊精)或经化学改性的衍生物如羟基烷基环糊精(包括2-和3-羟基丙基-β-环糊精)或其他溶解衍生物也可以用于增强如本文所提供的化合物的递送。可以制备含有在0.005%至100%范围内的如本文所提供的化学实体并且其余部分由无毒赋形剂构成的剂型或组合物。所考虑的组合物可以含有0.001%-100%、在一个实施方案中0.1%-95%、在另一实施方案中75%-85%、在另一实施方案中20%-80%的本文提供的化学实体。制备此类剂型的实际方法是本领域技术人员已知的或将清楚的;例如,参见Remington:The Science and Practice of Pharmacy,第22版(Pharmaceutical Press,London,UK.2012)。

[0164] 在一些实施方案中,本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物可以通过任何可接受的施用途径施用于有需要的受试者。可接受的施用途径包括但不限于经颊、皮肤、宫颈内、鼻窦内、气管内、肠内、硬膜外、间质、腹腔内、动脉内、支气管内、囊内、脑内、脑池内、冠状动脉内、皮内、导管内、十二指肠内、硬膜内、表皮内、食管内、胃内、牙龈内、回肠内、淋巴管内、髓内、脑膜内、肌肉内、卵巢内、腹膜内、前列腺内、肺内、窦内、脊柱内、滑膜内、睾丸内、鞘内、管内、瘤内、宫内、血管内、静脉内、鼻(例如,鼻内)、鼻胃、口服、肠胃外、经皮、经硬膜、直肠、呼吸(吸入)、皮下、舌下、粘膜下、外用、透皮、透粘膜、透气管、输尿管、尿道和阴道。在一些实施方案中,优选的施用途径为肠胃外(例如,瘤内)。

[0165] 在一些实施方案中,如本文所提供的本文公开的化合物(例如表1或表2的化合物或其药学上可接受的盐或溶剂化物)或其药物组合物可以配制用于肠胃外施用,例如被配制用于经由动脉内、胸骨内、颅内、静脉内、肌内、皮下或腹膜内途径注射。例如,此类组合物可以制备为可注射剂,作为液体溶液或混悬剂;也可以制备适合于在注射之前添加液体后制备溶液或混悬剂的固体形式;并且制剂也可以乳化。鉴于本公开文本,此类配制品的制备将是本领域技术人员已知的。在一些实施方案中,使用装置进行肠胃外施用。例如,此类装置可以包括针注射器、微针注射器、无针注射器和输注技术。

[0166] 在一些实施方案中,适合于注射的药物形式包括无菌水溶液或分散体;包含芝麻油、花生油或丙二醇的配制品;以及用于临时制备无菌可注射溶液或分散体的无菌粉末。在一些实施方案中,所述形式必须是无菌的并且必须在其可容易注射的程度上是流体的。在一些实施方案中,所述形式在制造和储存条件下应是稳定的并且必须在抵抗微生物(如细菌和真菌)的污染作用的情况下保存。

[0167] 在一些实施方案中,载体也可以是溶剂或分散介质,所述溶剂或分散介质含有例如水、乙醇、多元醇(例如,甘油、丙二醇和液体聚乙二醇等)、其合适的混合物以及植物油。在一些实施方案中,例如通过使用包衣(如卵磷脂),在分散液的情况下通过维持所希望的粒度,以及通过使用表面活性剂,可以维持适当的流动性。在一些实施方案中,防止微生物的作用可以通过各种抗细菌和抗真菌剂(例如,对羟基苯甲酸酯、氯丁醇、苯酚、山梨酸、硫柳汞等)来达到。在一些实施方案中,包括等渗剂,例如糖或氯化钠。在一些实施方案中,通过在组合物中使用延迟吸收的药剂(例如,单硬脂酸铝和明胶),可以延长可注射组合物的吸收。

[0168] 在一些实施方案中,无菌可注射溶液是通过将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)根据需要掺入具有以上列举的各种其他成分

的适当溶剂中,然后进行过滤杀菌来制备的。在一些实施方案中,分散体通过以下方式制备:将各种无菌活性成分掺入无菌媒介物中,所述媒介物含有基础分散介质和来自上文列举的那些成分的所需其他成分。在一些实施方案中,无菌粉末用于制备无菌可注射溶液。在一些实施方案中,制备方法是真空干燥和冷冻干燥技术,其由其先前无菌过滤的溶液产生活性成分加上任何另外希望成分的粉末。

[0169] 在一些实施方案中,在作为凝胶、乳膏、灌肠剂或直肠栓剂的直肠组合物中可使用的药理学上可接受的赋形剂包括但不限于以下中的任一个或多个:可可脂甘油酯、合成聚合物(如聚乙烯吡咯烷酮)、PEG(如PEG软膏)、甘油、经甘油处理的明胶、氢化植物油、泊洛沙姆、各种分子量的聚乙二醇与聚乙二醇脂肪酸酯的混合物、凡士林、无水羊毛脂、鲨鱼肝油、糖精钠、薄荷醇、甜杏仁油、山梨糖醇、苯甲酸钠、anoxid SBN、香草精油、气雾剂、苯氧基乙醇中的对羟基苯甲酸酯、甲基对氧基苯甲酸钠、丙基对氧基苯甲酸钠、二乙胺、卡波姆、卡波普(carbopol)、甲基氧基苯甲酸酯、聚乙二醇鲸蜡硬脂基醚、椰油酰基辛酰癸酸酯(cocoyl caprylocaprate)、异丙醇、丙二醇、液体石蜡、黄原胶、羧基-偏亚硫酸氢盐、依地酸钠、苯甲酸钠、偏亚硫酸氢钾、葡萄柚种子提取物、甲基磺酰基甲烷(MSM)、乳酸、甘氨酸、维生素(如维生素A和E)和乙酸钾。

[0170] 在一些实施方案中,栓剂可以通过将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或如本文所提供的药物组合物与合适的无刺激性赋形剂或载体(如可可脂、聚乙二醇、栓剂蜡)混合来制备,所述无刺激性赋形剂或载体(如可可脂、聚乙二醇、栓剂蜡)在环境温度下是固体但在体温下是液体并且因此在直肠中融化并释放活性化合物。在一些实施方案中,用于直肠施用的组合物呈灌肠剂的形式。

[0171] 在一些实施方案中,如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或其药物组合物被配制用于通过口服施用的方式(例如,固体或液体剂型)局部递送至消化道或GI道。

[0172] 在一些实施方案中,用于口服施用的固体剂型包括胶囊、片剂、丸剂、散剂和颗粒剂。在一些实施方案中,将本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)与一种或多种药学上可接受的赋形剂如柠檬酸钠或磷酸二钙和/或以下物质混合:a)填充剂或增量剂,如淀粉、乳糖、蔗糖、葡萄糖、甘露糖醇和硅酸;b)粘合剂,例如像羧甲基纤维素、海藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖和阿拉伯胶;c)保湿剂,如甘油;d)崩解剂,如琼脂、碳酸钙、马铃薯或木薯淀粉、海藻酸、某些硅酸盐和碳酸钠;e)溶液阻滞剂,如石蜡;f)吸收促进剂,如季铵化合物;g)润湿剂,例如像鲸蜡醇和单硬脂酸甘油酯;h)吸附剂,如高岭土和膨润土;以及i)润滑剂,如滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、月桂基硫酸钠及其混合物。例如,在胶囊、片剂及丸剂的情况下,剂型还可以包含缓冲剂。在一些实施方案中,类似类型的固体组合物也可作为填充剂用于使用如乳糖或奶糖以及高分子量聚乙二醇等的赋形剂的软和硬填充明胶胶囊中。

[0173] 在一些实施方案中,药物组合物将采用如丸剂或片剂的单位剂型的形式,并且因此,所述组合物可以含有与如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)一起的稀释剂,如乳糖、蔗糖、磷酸二钙等;润滑剂,如硬脂酸镁等;以及粘合剂,如淀粉、阿拉伯胶、聚乙烯吡咯烷酮、明胶、纤维素、纤维素衍生物等。在一些实施方案中,将作为另一种固体剂型的散剂、球形造粒物(marume)、溶液或混悬

剂(例如,在碳酸亚丙酯、植物油、PEG、泊洛沙姆124或三酸甘油酯中)包囊在胶囊(明胶或纤维素基质胶囊)中。在一些实施方案中,还考虑了如本文所提供的一种或多种化合物和药物组合物或额外活性剂在物理上分离的单位剂型;例如,具有各药物的颗粒的胶囊(或胶囊中的片剂);二层片剂;二室囊形片(gel caps)等。在一些实施方案中,还考虑了肠溶包衣或延迟释放口服剂型。

[0174] 在一些实施方案中,其他生理学上可接受的化合物可以包含湿润剂、乳化剂、分散剂或特别可用于防止微生物生长或活动的防腐剂。例如,各种防腐剂是熟知的并且包括例如苯酚和抗坏血酸。

[0175] 在一些实施方案中,赋形剂是无菌的并且一般不含不希望的物质。例如,这些组合物可以通过常规的熟知的杀菌技术来杀菌。在一些实施方案中,对于各种口服剂型赋形剂,如片剂及胶囊,不需要杀菌。例如,美国药典/国家处方集(United States Pharmacopeia/National Formulary,USP/NF)标准可以是足够的。

[0176] 在一些实施方案中,如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或其药物组合物被配制用于眼部施用。在一些实施方案中,眼部组合物可以包括而不限于以下中的一种或多种:粘精(viscogen)(例如,羧甲基纤维素、甘油、聚乙烯吡咯烷酮、聚乙二醇);稳定剂(例如,普洛尼克(pluronic)(三嵌段共聚物)、环糊精);防腐剂(例如,苯扎氯铵(benzalkonium chloride)、ETDA、SofZia(硼酸、丙二醇、山梨糖醇和氯化锌;Alcon Laboratories,Inc.)、Purite(稳定化的氧氯复合物;Allergan,Inc.))。

[0177] 在一些实施方案中,如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)或其药物组合物被配制用于皮肤或粘膜的局部施用(例如,经皮或透皮)。在一些实施方案中,外用组合物可以包括软膏和乳膏。在一些实施方案中,软膏是典型地基于矿脂或其他石油衍生物的半固体制剂。在一些实施方案中,含有所选活性剂的乳膏典型地是粘稠液体或半固体乳剂,常常是水包油或油包水的。例如,乳膏基质典型地是可水洗的,并且含有油相、乳化剂和水相。例如,油相,有时也称作“内部”相,通常由矿脂和脂肪醇如鲸蜡醇或硬脂醇构成;尽管不是必需的,但水相的体积通常超过油相,并且通常含有保湿剂。在一些实施方案中,乳膏配制品中的乳化剂通常是非离子、阴离子、阳离子或两性表面活性剂。在一些实施方案中,像其他载体或媒介物那样,软膏基质应是惰性、稳定、无刺激性且不致敏的。

[0178] 在任一个前述实施方案中,如本文所提供的药物组合物可以包含以下中的一种或多种:脂质、双层间交联多层囊泡、生物可降解的基于聚(D,L-乳酸-共-乙醇酸)[PLGA]的或基于聚酐的纳米颗粒或微颗粒,以及纳米多孔颗粒负载型脂质双层。

[0179] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)的剂量是基于多种因素来确定的,所述因素包括但不限于受试者的类型、年龄、体重、性别、医学病症,受试者的医学病症的严重程度,施用途径以及化合物或其药学上可接受的盐或溶剂化物的活性。在一些实施方案中,用于特定情况的适当剂量可以通过医学领域技术人员来确定。在一些实施方案中,总每日剂量可以分成多份并且在一整天内以多份施用或借助提供连续递送的方式施用。

[0180] 在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可

接受的盐或溶剂化物)以约0.01至约1000mg的剂量施用。例如,约0.1至约30mg、约10至约80mg、约0.5至约15mg、约50mg至约200mg、约100mg至约300mg、约200至约400mg、约300mg至约500mg、约400mg至约600mg、约500mg至约800mg、约600mg至约900mg、或约700mg至约1000mg。在一些实施方案中,剂量是治疗有效量。

[0181] 在一些实施方案中,将如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)以如下剂量施用:约0.0002mg/Kg至约100mg/Kg(例如,约0.0002mg/Kg至约50mg/Kg;约0.0002mg/Kg至约25mg/Kg;约0.0002mg/Kg至约10mg/Kg;约0.0002mg/Kg至约5mg/Kg;约0.0002mg/Kg至约1mg/Kg;约0.0002mg/Kg至约0.5mg/Kg;约0.0002mg/Kg至约0.1mg/Kg;约0.001mg/Kg至约50mg/Kg;约0.001mg/Kg至约25mg/Kg;约0.001mg/Kg至约10mg/Kg;约0.001mg/Kg至约5mg/Kg;约0.001mg/Kg至约1mg/Kg;约0.001mg/Kg至约0.5mg/Kg;约0.001mg/Kg至约0.1mg/Kg;约0.01mg/Kg至约50mg/Kg;约0.01mg/Kg至约25mg/Kg;约0.01mg/Kg至约10mg/Kg;约0.01mg/Kg至约5mg/Kg;约0.01mg/Kg至约1mg/Kg;约0.01mg/Kg至约0.5mg/Kg;约0.01mg/Kg至约0.1mg/Kg;约0.1mg/Kg至约50mg/Kg;约0.1mg/Kg至约25mg/Kg;约0.1mg/Kg至约10mg/Kg;约0.1mg/Kg至约5mg/Kg;约0.1mg/Kg至约1mg/Kg;约0.1mg/Kg至约0.5mg/Kg)。在一些实施方案中,将如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)以约100mg/Kg的剂量施用。

[0182] 在一些实施方案中,本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)的前述剂量可以在每日基础上(例如,作为单剂量或作为两个或更多个分剂量)或在非每日基础上(例如,每隔一天、每两天、每三天、每周一次、每周两次、每两周一次、一个月一次)施用。

[0183] 在一些实施方案中,如本文所提供的本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)的施用时间段是1天、2天、3天、4天、5天、6天、7天、8天、9天、10天、11天、12天、13天、14天、3周、4周、5周、6周、7周、8周、9周、10周、11周、12周、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更长时间。在一些实施方案中,停止施用的时间段是1天、2天、3天、4天、5天、6天、7天、8天、9天、10天、11天、12天、13天、14天、3周、4周、5周、6周、7周、8周、9周、10周、11周、12周、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更长时间。在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)施用于受试者一段时间,随后是停止施用本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)的单独时间段。在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)施用持续第一时间段,以及在第一时间段后的第二时间段,其中在第二时间段期间停止施用,随后是开始施用本文公开的化合物或其药学上可接受的盐或溶剂化物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)的第三时间段,并且随后是在第三时间段后的第四时间段,在所述第四时间段停止施用。例如,施用本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)的时间段、随后停止施用的时间段在确定或未确定的时间段内重复。在一些实施方案中,施用时间段是1天、2天、3天、4天、5天、6天、7天、8天、9天、10天、11天、12天、13天、14天、3周、4周、5周、6周、7周、8周、9周、10周、11周、12周、4个月、5个月、6个

月、7个月、8个月、9个月、10个月、11个月、12个月或更长时间。在一些实施方案中,停止施用的时间段是1天、2天、3天、4天、5天、6天、7天、8天、9天、10天、11天、12天、13天、14天、3周、4周、5周、6周、7周、8周、9周、10周、11周、12周、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更长时间。

[0184] 在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)口服施用于受试者,每天一或多次(例如,每天一次、每天两次、每天三次、每天四次或单次每日剂量)。

[0185] 在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)通过肠胃外施用而施用于受试者,每天一或多次(例如,1至4次,每天一次、每天两次、每天三次、每天四次或单次每日剂量)。

[0186] 在一些实施方案中,将本文公开的化合物(例如,表1或表2的化合物或其药学上可接受的盐或溶剂化物)每周通过肠胃外施用而施用于受试者。

化合物的合成

[0187] 本公开文本的化合物可以使用例如以下通用方法和程序从容易获得的起始材料制备。将理解,除非另有说明,否则在得到某种工艺条件(即,反应温度、时间、反应物的摩尔比、溶剂、压力等)的情况下,也可以使用其他工艺条件。最佳反应条件可以随所用的反应物或溶剂而变化,但是此类条件可以由本领域技术人员通过常规优化程序确定。

[0188] 另外,如对于本领域技术人员而言将清楚的,常规保护基团可能是必要的以防止某些官能团经历不希望的反应。用于各种官能团的合适保护基团以及用于保护和去保护某种官能团的合适条件是本领域熟知的。例如,在T.W.Greene和G.M.Wuts(1999)Protecting Groups in Organic Synthesis,第3版,Wiley,New York以及其中引用的参考文献中描述了许多保护基团。

[0189] 此外,本公开文本的化合物可以含有一个或多个手性中心。因此,如果需要,可以将此类化合物制备或分离为纯的立体异构体,即作为单独的对映异构体或非对映异构体或者作为立体异构体富集的混合物。除非另有指示,否则所有此类立体异构体(和富集的混合物)都被包括在本公开文本的范围内。纯的立体异构体(或富集的混合物)可以使用例如本领域熟知的光活性起始材料或立体选择性试剂来制备。可替代地,可以使用例如手性柱色谱法、手性拆分剂等来分离此类化合物的外消旋混合物。

[0190] 用于以下反应的起始材料通常是已知的化合物,或者可以通过已知的程序或其明显的修改来制备。例如,许多起始材料可从商业供应商(如Aldrich Chemical Co.(美国威斯康辛州密尔沃基)、Bachem(美国加利福尼亚州托伦斯)、EMKA Chemie Gmbh&Co.KG(德国埃青)或Millipore Sigma(美国密苏里州圣路易斯))处获得。其他起始材料可以通过在标准参考文本中描述的程序或其明显的修改来制备,所述标准参考文本如Fieser and Fieser's Reagents for Organic Synthesis,第1-15卷(John Wiley,and Sons,1991)、Rodd's Chemistry of Carbon Compounds,第1-5卷和增刊(Elsevier Science Publishers,1989)、Organic Reactions,第1-40卷(John Wiley,and Sons,1991)、March's Advanced Organic Chemistry(John Wiley,and Sons,第5版,2001)和Larock's Comprehensive Organic Transformations(VCH Publishers Inc.,1989)。

一般合成

[0191] 本文所述的化合物的典型实施方案可以使用以下所述的通用反应方案来合成。鉴于本文的描述，应清楚的是，可以通过用具有类似结构的其他材料替代起始材料来改变通用方案，以产生相应不同的产物。以下合成的描述提供了关于起始材料可以如何变化以提供相应产物的许多实施例。鉴于定义了取代基团的所希望的产物，通常可以通过检查确定必需的起始原料。起始材料通常从商业来源获得或者使用公开的方法合成。为了合成作为本公开文本中所述的实施方案的化合物，对待合成的化合物的结构的检查将提供每个取代基团的身份。鉴于本文的实施例，通过简单的检查过程，最终产物的身份通常将使必需的起始材料的身份变得清楚。通常，本文所述的化合物在室温和压力下典型地是稳定的和可分离的。

实施例

[0192] 包括以下实施例以展示本公开文本的具体实施方案。本领域技术人员应理解，以下实施例中公开的技术代表在本公开文本的实践中很好地起作用的技术，并且因此可以被认为是构成其实践的具体模式。然而，根据本公开文本，本领域技术人员应理解，在不脱离本公开文本的精神和范围的情况下，可以在所公开的具体实施方案中进行许多改变并且仍然获得相同或相似的结果。

[0193] 缩写(如本文所用)：

AcOH	乙酸
AIBN	偶氮二异丁腈
aq.	水性
CCl_4	四氯化碳
CH_3CN	乙腈
CH_2Cl_2或DCM	二氯甲烷
DBU	1,8-二氮杂双环[5.4.0]十一-7-烯
DIAD	偶氮二甲酸二异丙酯
DIBAL-H	二异丁基氢化铝
DIEA或DIPEA	*N*-乙基-*N*,*N*-二异丙胺
DMAP	4-(二甲基氨基)吡啶
DMF	*N*,*N*-二甲基-甲酰胺
DMSO	二甲基亚砜
EtOAc	乙酸乙酯
EtOH	乙醇
Et_3N	三乙胺
h	小时
HCl	盐酸
H_2O	水
HPLC	高效液相色谱法
$[Ir(COD)(OMe)]_2$	(1,5-环辛二烯)(甲氧基)铱(I)二聚体
K_2CO_3	碳酸钾

$K_2OsO_4.2H_2O$	锇酸钾
$LiBH_4$	硼氢化锂
MeI	碘甲烷
MeOH	甲醇
MsCl	甲磺酰氯
Na_2CO_3	碳酸钠
$NaHCO_3$	碳酸氢钠
$NaIO_4$	高碘酸钠
NaCN	氰化钠
Na_2SO_4	硫酸钠
NaH	氢化钠
NaH_2PO_4	磷酸二氢钠
NaOH	氢氧化钠
NBS	溴代丁二酰亚胺
n-BuLi	正丁基锂
NH_4Cl	氯化铵
NMP	1-甲基-吡咯烷-2-酮
$Pd_2(dba)_3$	三(二亚苄基丙酮)二钯
$Pd(dppf)Cl_2.CH_2Cl_2$	[1,1'-双(二苯基膦基)-二茂铁]氯化钯(II)-二氯甲烷络合物
$Pd(OAc)_2$	乙酸钯(II)
PE	石油醚
PPh_3	三苯基膦
Prep.	制备型
PTSA	对甲苯磺酸
sat.	饱和的
s-Phos	二环己基-(2',6'-二甲氧基联苯-2-基)-膦
t-BuOK	叔丁醇钾
t-BuXphos	二叔丁基(2',4',6'-三异丙基-[1,1'-联苯]-2-基)膦
TBAF	四丁基氟化铵
TBS	叔丁基二甲基甲硅烷基
TMSCl	氯三甲基硅烷
TFA	三氟乙酸
THF	四氢呋喃
TLC	薄层色谱法
Xantphos	4,5-双(二苯基膦基)-9,9-二甲基呫吨
Xphos	二环己基(2',4',6'-三异丙基-[1,1'-联苯]-2-基)膦

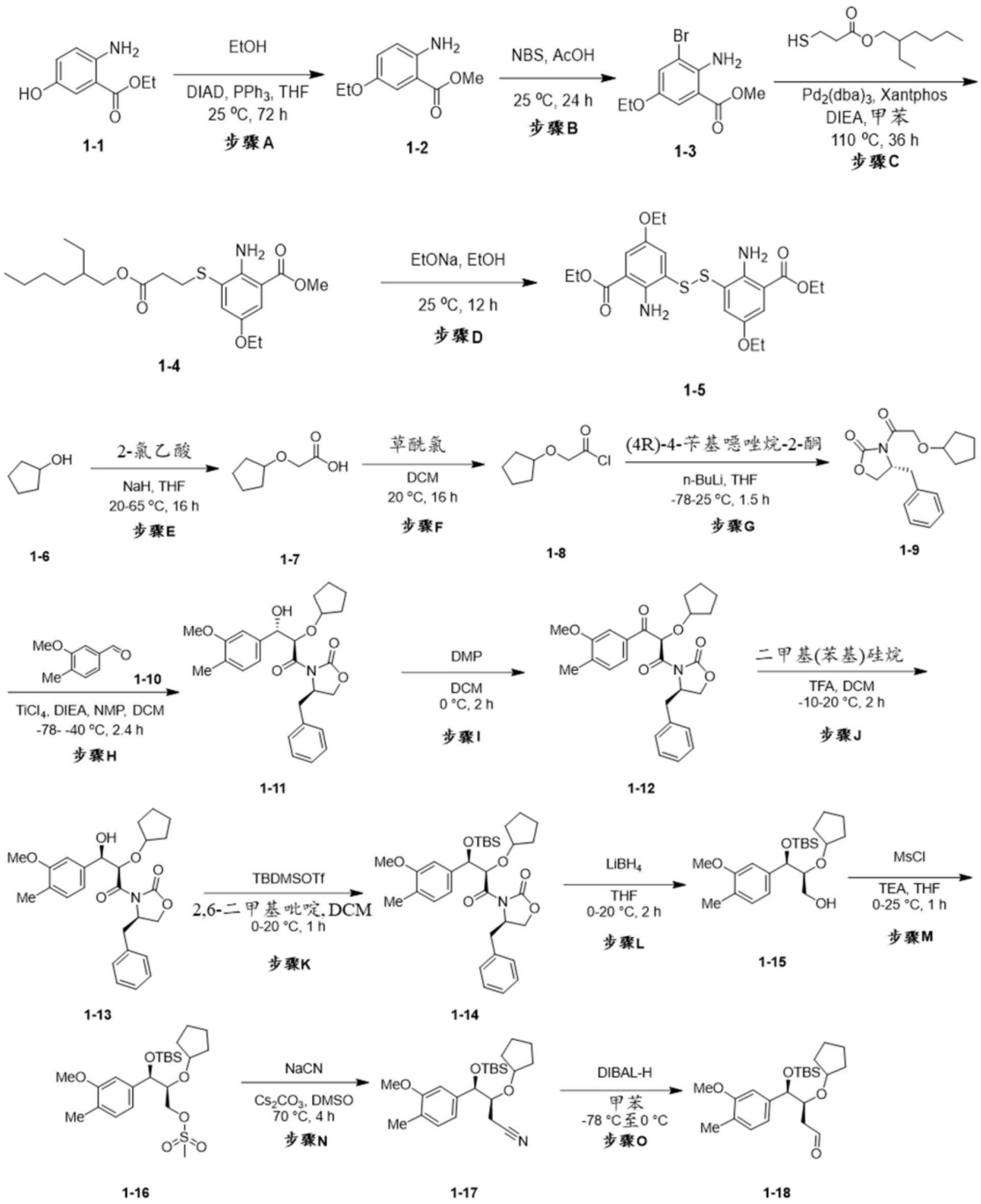
[0194] 一般信息:所有蒸发或浓缩均在真空中用旋转蒸发器进行。在室温下在真空中(1-5mmHg)干燥分析样品。在硅胶板上进行薄层色谱法(TLC),用紫外光(214和254nm)可视化斑点。使用硅胶(100-200目)通过柱和快速色谱法进行纯化。溶剂体系报告为按体积的混合物。NMR谱是在Bruker 400或Varian(400MHz)波谱仪上记录的。^{1}H化学位移以按ppm计的δ值报告,其中氘化溶剂作为内标。数据如下报告:化学位移、多重性(s=单峰,d=双重峰,t=三重峰,q=四重峰,br=宽峰,m=多重峰)、耦合常数(Hz)、积分。除非另有说明,否则LCMS谱是在SHIMADZU LC20-MS2020或Agilent 1260系列6125B质谱仪或Agilent 1200系列、具有电喷雾电离的6110或6120质谱仪上获得的。

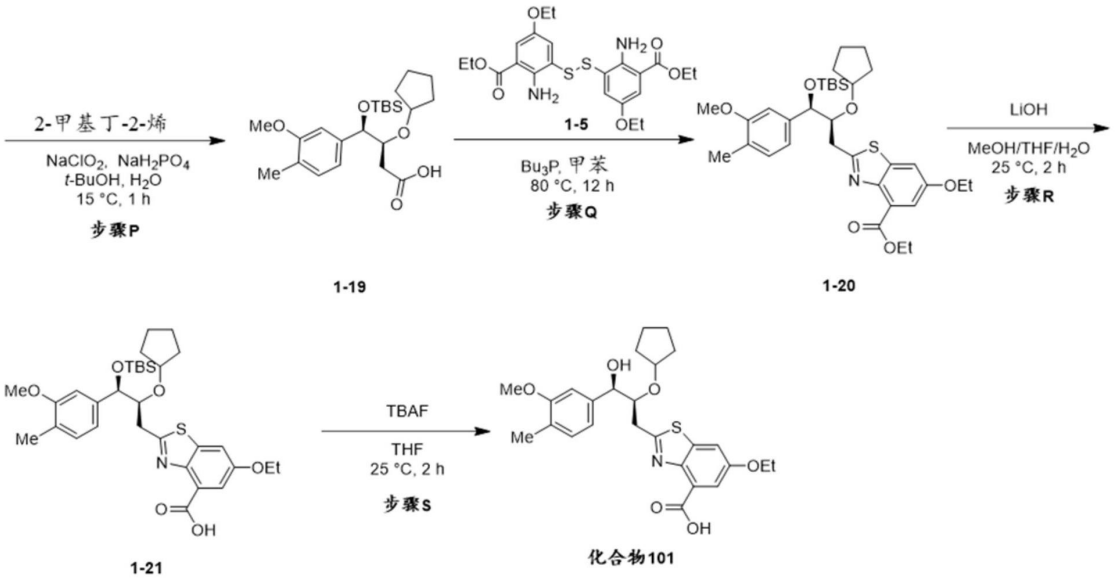
实施例A1

2-((2S,3R)-2-(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲基苯基)丙基)-6-乙氧

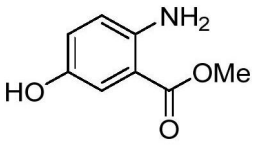
基苯并[d]噻唑-4-

甲酸(化合物101)



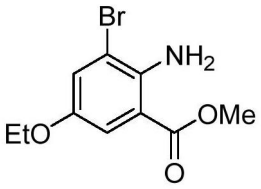


[0195] 步骤A:2-氨基-5-乙氧基苯甲酸甲酯



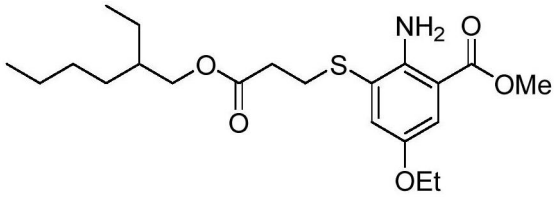
[0196] 在25℃下向2-氨基-5-羟基-苯甲酸甲酯(10.0g,59.8mmol)、EtOH(5.51g,6.99mL)和PPh_3(31.4g,120mmol)在THF(150mL)中的溶液中逐滴添加DIAD(24.2g,23.3mL)。将所得反应混合物在25℃下搅拌72h。在减压下去除溶剂以得到残余物。将残余物通过快速硅胶色谱法(ISCO®;120g SepaFlash®硅胶快速柱,在100mL/min下的0-15% EtOAc/PE梯度洗脱液)纯化以得到2-氨基-5-乙氧基-苯甲酸甲酯(10.9g,93.0%产率)。^{1}H NMR(400MHz,DMSO-d_6)δ7.17(d,J=2.8Hz,1H),6.97(dd,J=8.8,3.2Hz,1H),6.74(d,J=8.8Hz,1H),6.29(s,2H),3.89(q,J=6.8Hz,2H),3.78(s,3H),1.27(t,J=7.0Hz,3H)。

[0197] 步骤B:2-氨基-3-溴-5-乙氧基苯甲酸甲酯



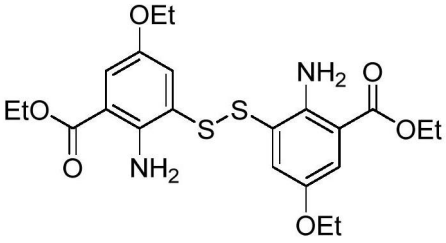
[0198] 向2-氨基-5-乙氧基-苯甲酸甲酯(10.9g,55.6mmol)在AcOH(80mL)中的溶液中添加NBS(9.90g,55.6mmol)。将所得混合物在25℃下搅拌24h。将反应混合物倒入水(60mL)中并搅拌10min。将水相用EtOAc(30mL x 3)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤并且在真空中浓缩。将残余物通过快速硅胶色谱法(ISCO®;120gSepaFlash®硅胶快速柱,在100mL/min下的0-5% EtOAc/PE梯度洗脱液)纯化以得到2-氨基-3-溴-5-乙氧基-苯甲酸甲酯(6.65g,43.7%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.32(d,J=2.8Hz,1H),7.20(d,J=2.8Hz,1H),5.59(brs,2H),3.87(q,J=7.0Hz,2H),3.80(s,3H),1.29(t,J=7.0Hz,3H)。

[0199] 步骤C:2-氨基-5-乙氧基-3-((3-((2-乙基己基)氧基)-3-氧代丙基)硫代)苯甲酸甲酯



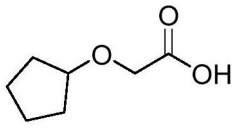
[0200] 向2-乙基己基3-硫烷基丙酸酯(5.30g,24.3mmol)和2-氨基-3-溴-5-乙氧基-苯甲酸甲酯(6.65g,24.3mmol)在甲苯(80mL)中的溶液中添加$Pd_2(dba)_3$(1.11g,1.21mmol)、Xantphos(1.40g,2.43mmol)和DIEA(7.84g,60.7mmol,10.6mL)。将混合物在110℃下搅拌36h。将残余物倒入水(150mL)中并且搅拌10min。将水相用EtOAc(80mLx3)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤并且在真空中浓缩。将残余物通过快速硅胶色谱法(ISCO®;120gSepaFlash®硅胶快速柱,在100mL/min下的以0-5% EtOAc/PE梯度洗脱液)纯化以得到2-氨基-5-乙氧基-3-[3-(2-乙基己基)-3-氧代-丙基]硫烷基-苯甲酸甲酯(8.29g,83.0%产率)。

[0201] 步骤D:2-氨基-5-乙氧基-3-[(3-乙氧基-5-甲氧基羰基-苯基)二硫烷基]苯甲酸甲酯



[0202] 向2-氨基-5-乙氧基-3-[2-(2-乙基己氧基)-2-氧代-乙基]硫烷基-苯甲酸甲酯(8.29g,20.9mmol)在EtOH(50mL)中的溶液中添加EtONa(9.22g,27.1mmol,在EtOH中20%)。将反应混合物在25℃下搅拌12h。将残余物用水(100mL)稀释,用37% HCl酸化至pH=6,用EtOAc(100mL x 3)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤并且在真空中浓缩。将残余物通过快速硅胶色谱法(ISCO®;120gSepaFlash®硅胶快速柱,在100mL/min下的0-5% EtOAc/PE梯度洗脱液)纯化以得到2-氨基-5-乙氧基-3-[(3-乙氧基-5-甲氧基羰基-苯基)二硫烷基]苯甲酸甲酯(1.09g,12.0%产率)。^1H NMR(400MHz,$CDCl_3$)δ7.46(d,J=3.2Hz,2H),6.84(d,J=3.2Hz,2H),6.37(brs,4H),4.27(q,J=7.2Hz,4H),3.75(q,J=6.8Hz,4H),1.32(t,J=7.0Hz,6H),1.24(t,J=7.0Hz,6H)。

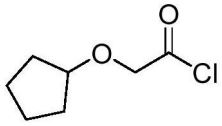
[0203] 步骤E:2-(环戊基氧基)乙酸



[0204] 在0℃下向环戊醇(3g,34.83mmol)在THF(50mL)中的溶液中添加NaH(2.79g,69.66mmol,60%纯度)。在60℃下搅拌30min后,然后在25℃下将2-氯乙酸(3.29g,34.83mmol)缓慢添加到反应混合物中。将所得混合物在60℃下搅拌16h。冷却后,将反应混合物用H_2O(10mL)淬灭,用H_2O(50mL)稀释,将pH值用1N HCl调节至5。将混合物用EtOAc(40mL x 3)萃取。将合并的有机层用盐水(50mL x 3)洗涤,经无水Na_2SO_4干燥,过滤并且在减压下浓缩以得到残余物。将残余物通过硅胶柱色谱法(PE/EtOAc=1/0至1/1)纯化以得到2-(环

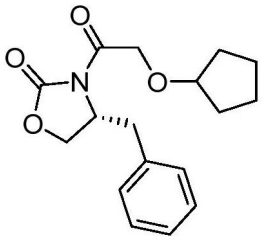
戊基氧基)乙酸(3.7g,73%产率)。^{1}H NMR(400MHz,DMSO-d6)δ4.21-4.19(m,1H),3.94(s,2H),1.71-1.28(m,8H)。

[0205] 步骤F:2-(环戊基氧基)乙酰氯



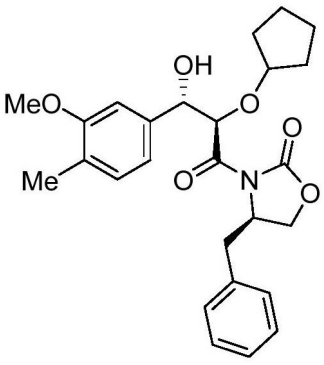
[0206] 向2-(环戊基氧基)乙酸(3.7g,25.66mmol)在DCM(20mL)中的溶液中添加草酰氯(4.89g,38.50mmol)和DMF(0.1mL)。然后将混合物在25℃下搅拌1h。将反应混合物在减压下浓缩,以得到2-(环戊基氧基)乙酰氯(4.17g,粗品),将其无需进一步纯化直接用于下一步骤。

[0207] 步骤G:(R)-4-苄基-3-(2-(环戊基氧基)乙酰基)噁唑烷-2-酮



[0208] 在-78℃下在N_2下向(4R)-4-苄基噁唑烷-2-酮(6.82g,38.47mmol)在THF(30mL)中的溶液中逐滴添加n-BuLi(14.36mL,35.9mmol,在己烷中的2.5M溶液)。添加后,在-78℃下将2-(环戊基氧基)乙酰氯(4.17g,25.64mmol)在THF(8mL)中的溶液添加到混合物中。将所得混合物在25℃下搅拌2h。然后将反应混合物通过饱和NH_4Cl水溶液(50mL)淬灭,用EtOAc(30mL x 3)萃取。将合并的有机层用水(20mL x 3)洗涤,经Na_2SO_4干燥,过滤并且在减压下浓缩以得到残余物。将残余物通过硅胶柱色谱法(PE/EtOAc=1/0至1/1)纯化以得到(4R)-4-苄基-3-[2-(环戊基氧基)乙酰基]噁唑烷-2-酮(2.14g,23%产率)。LC-MS:m/z 304.1(M+H)$^+$。

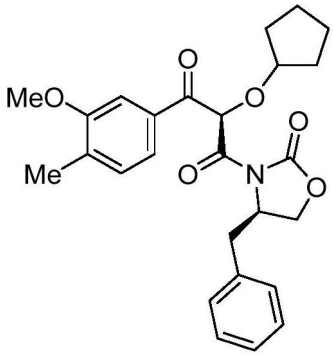
[0209] 步骤H:(R)-4-苄基-3-((2R,3S)-2-(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲基苯基)丙酰基)噁唑烷-2-酮



[0210] 在-78℃下在氮气下向(R)-4-苄基-3-(2-(环戊基氧基)乙酰基)噁唑烷-2-酮(1.8g,5.93mmol)在DCM(45mL)中的溶液中添加$TiCl_4$(683μL,6.23mmol)。将混合物在-78℃下搅拌15min。然后在-78℃下逐滴添加DIEA(2.58mL,14.8mmol)。将所得混合物在-78℃下搅拌40分钟。然后逐滴添加NMP(577μL,5.93mmol)。将反应混合物在-78℃下在氮气下搅拌10min。然后逐滴添加在干DCM(10mL)中的3-甲氧基-4-甲基苯甲醛(980mg,6.53mmol)。将所

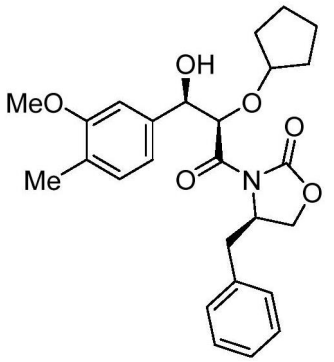
得混合物在-78℃下在氮气下搅拌2h。然后将反应混合物用饱和NH_4Cl水溶液(50mL)淬灭,用DCM(60mL x 3)萃取。将有机层经无水Na_2SO_4干燥,过滤并且浓缩以得到残余物。将残余物通过快速硅胶色谱法(ISCO®;40g Sepa Flash®硅胶快速柱,在40mL/min下的0-45% EtOAc/PE梯度洗脱液)纯化以得到(R)-4-苄基-3-((2R,3S)-2-(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲苯基)丙酰基)噁唑烷-2-酮(2.27g,84.4%产率)。LC-MS:m/z 476.2(M+Na)$^+$。

[0211] 步骤I:(R)-1-((R)-4-苄基-2-氧代噁唑烷-3-基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙烷-1,3-二酮



[0212] 在0℃下,向(R)-4-苄基-3-((2R,3S)-2-(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲基苯基)丙酰基)噁唑烷-2-酮(2.27g,5.01mmol)在DCM(30mL)中的混合物中分批添加戴斯-马丁高碘烷(4.25g,10.0mmol)。将反应混合物在0℃下搅拌2h。然后将混合物用H_2O(50mL)和DCM(50mL)淬灭。将混合物通过硅藻土过滤并且用DCM(50mL x 2)萃取。将有机层经Na_2SO_4干燥,过滤并且在真空下浓缩。将残余物通过快速硅胶色谱法(ISCO®;40g Sepa Flash®硅胶快速柱,在40mL/min下的0-35% EtOAc/PE梯度洗脱液)纯化以得到(R)-1-((R)-4-苄基-2-氧代噁唑烷-3-基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙烷-1,3-二酮(2.2g,97.4%产率)。LC-MS:m/z 474.1(M+Na)$^+$。

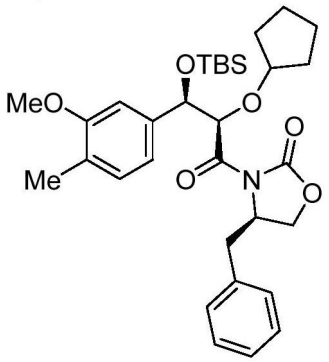
[0213] 步骤J:(R)-4-苄基-3-((2R,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙酰基)噁唑烷-2-酮



[0214] 在-10℃下,向(R)-1-((R)-4-苄基-2-氧代噁唑烷-3-基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙烷-1,3-二酮(2.2g,4.87mmol)在TFA(21.7mL)和DCM(22mL)中的混合物中逐滴添加二甲基(苯基)硅烷(2.27mL,14.6mmol)。将反应混合物在-10℃下搅拌2h。将溶液倒入饱和$NaHCO_3$水溶液(200mL)中,用DCM(30mL x 3)萃取。将合并的有机物经无水Na_2SO_4干燥,过滤并浓缩。将残余物通过快速硅胶色谱法(ISCO®;40g SepaFlash®硅胶快速柱,在40mL/min下的0-50% EtOAc/PE梯度洗脱液)纯化以得到(R)-4-苄基-3-((2R,3R)-2-

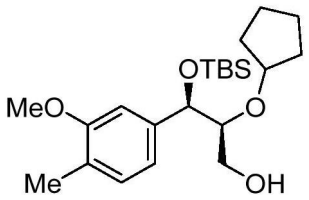
(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲基苯基)丙酰基)噁唑烷-2-酮(1.85g,83.7%产率)。LC-MS:m/z 476.1(M+Na)$^+$。

[0215] 步骤K:(R)-4-苄基-3-((2R,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙酰基)噁唑烷-2-酮



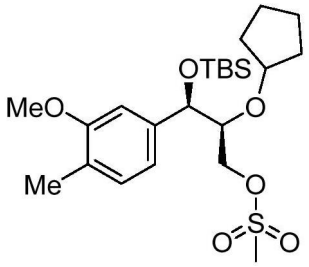
[0216] 在0℃下,向(R)-4-苄基-3-((2R,3R)-2-(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲基苯基)丙酰基)噁唑烷-2-酮(1.85g,4.08mmol)在DCM(15mL)和2,6-二甲基吡啶(950μL,8.16mmol)中的混合物中添加[叔丁基(二甲基)甲硅烷基]三氟甲磺酸酯(1.88mL,8.16mmol)。将反应混合物在0℃下搅拌2h。然后将混合物用H_2O(50mL)淬灭,用DCM(50mL x 3)萃取。将有机层用H_2O(50mL x 2)洗涤,经无水Na_2SO_4干燥,并且在真空下浓缩。将残余物通过快速硅胶色谱法(ISCO®;20g SepaFlash®硅胶快速柱,在35mL/min下的0-10% EtOAc/PE梯度洗脱液)纯化以得到(4R)-4-苄基-3-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-甲基-苯基)丙酰基]噁唑烷-2-酮(2.2g,产率95.0%)。

[0217] 步骤L:(2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙-1-醇



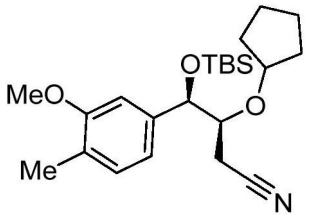
[0218] 在0℃下,在N_2下向$LiBH_4$(9.69mL,38.76mmol,在THF中的4M溶液)在THF(10mL)中的混合物中逐滴添加H_2O(15.4mg,852μmol)。将混合物在0℃下搅拌0.5h。然后逐滴添加(R)-4-苄基-3-((2R,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙酰基)噁唑烷-2-酮(2.2g,3.87mmol)在THF(20mL)中的溶液。将反应混合物温热至15℃并且在15℃下搅拌16h。将反应混合物用1M HCl水溶液小心地中和,用EtOAc(30mL x 3)萃取。将有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过快速硅胶色谱法(ISCO®;40g SepaFlash®硅胶快速柱,在40mL/min下的0-10% EtOAc/PE梯度洗脱液)纯化以得到(2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙-1-醇(1.26g,82.4%产率)。^1H NMR(400MHz,$CDCl_3$)δ7.04(d,J=7.2Hz,1H),6.85(s,1H),6.79(d,J=7.6Hz,1H),4.61(d,J=6.8Hz,1H),3.82(s,3H),3.81-3.70(m,3H),3.36-3.35(m,1H),2.20(s,3H),1.58-1.26(m,8H),0.89(s,9H),0.05(s,3H),-0.16(s,3H)。

[0219] 步骤M:(2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙基甲磺酸酯



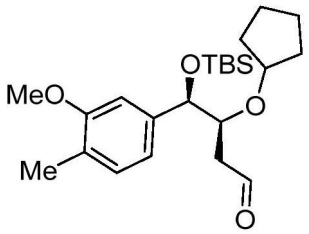
[0220] 在0℃下向(2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙-1-醇(1.26g,3.19mmol)在DCM(20mL)和TEA(667μL,4.79mmol)中的混合物中逐滴添加MsCl(439mg,3.83mmol,297μL)。将反应混合物在0℃下搅拌0.5h。将混合物用饱和$NaHCO_3$(50mL)水溶液淬灭,用DCM(20mL x 3)萃取。将有机层用0.5N HCl(20mL x 2)、盐水(20mL x 2)洗涤,经Na_2SO_4干燥,并且在真空下浓缩。将残余物通过快速硅胶色谱法(ISCO®;20g SepaFlash®硅胶快速柱,在35mL/min下的0-15% EtOAc/PE梯度洗脱液)纯化以得到(2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙基甲磺酸酯(1.42g,94.1%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.05(d,J=7.6Hz,1H),6.84(s,1H),6.79-6.76(m,1H),4.65(d,J=5.6Hz,1H),4.41-4.27(m,2H),3.82(s,4H),3.57-3.56(m,1H),2.99(s,3H),2.20(s,3H),1.61-1.30(m,8H),0.89(s,9H),0.07(s,3H),-0.14(s,3H)。

[0221] 步骤N:(3S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3-甲氧基-4-甲基苯基)丁腈



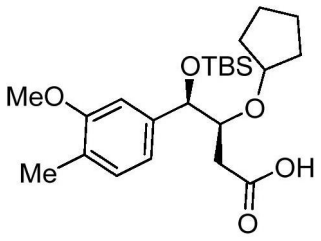
[0222] 向[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-甲基-苯基)丙基]甲磺酸酯(6.0g,12.69mmol)在DMSO(60mL)中的溶液中添加NaCN(3.11g,63.46mmol)。将混合物在85℃下搅拌3h。冷却后,将混合物用H_2O(60mL)淬灭,用EtOAc(60mL x 2)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过硅胶柱(PE/EtOAc=10/1)纯化以得到(3S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3-甲氧基-4-甲基苯基)丁腈(4g,78.1%产率)。LC-MS:m/z 426.2$(M+Na)^+$。

[0223] 步骤O:(3S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3-甲氧基-4-甲基苯基)丁醛



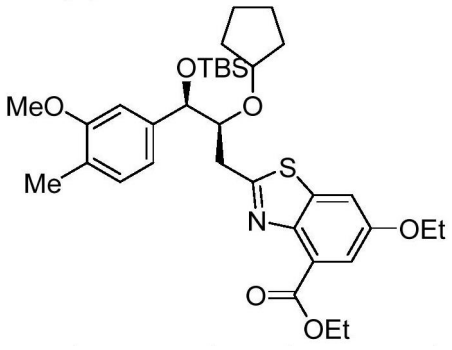
[0224] 在-78℃下向(3S,4R)-4-[叔丁基(二甲基)甲硅烷基]氧基-3-(环戊基氧基)-4-(3-甲氧基-4-甲基-苯基)丁腈(4.0g,9.91mmol)在甲苯(50mL)中的溶液中添加DIBAL-H(19.82mL,19.82mmol)。将反应混合物在0℃下搅拌1h。然后将混合物用酒石酸钾钠溶液(50mL)淬灭,用EtOAc(50mL x 3)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩以得到粗(3S,4R)-4-[叔丁基(二甲基)甲硅烷基]氧基-3-(环戊基氧基)-4-(3-甲氧基-4-甲基-苯基)丁醛(4.0g,99.2%产率),将其无需进一步纯化用于下一步骤。

[0225] 步骤P:(3S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3-甲氧基-4-甲基苯基)丁酸



[0226] 向(3S,4R)-4-[叔丁基(二甲基)甲硅烷基]氧基-3-(环戊基氧基)-4-(3-甲氧基-4-甲基-苯基)丁醛(4.0g,9.84mmol)在t-BuOH(40mL)和H_2O(10mL)中的溶液中添加NaH_2PO_4(1.18g,9.84mmol)、亚氯酸钠(3.20g,35.41mmol)和2-甲基丁-2-烯(3.10g,44.27mmol)。将反应混合物在25℃下搅拌1h。然后将混合物用H_2O(60mL)淬灭,用EtOAc(60mL x 2)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过硅胶柱(PE/EtOAc=10/1)纯化以得到(3S,4R)-4-[叔丁基(二甲基)甲硅烷基]氧基-3-(环戊基氧基)-4-(3-甲氧基-4-甲基-苯基)丁酸(1.6g,38.5%产率)。LC-MS:m/z 445.1$(M+Na)^+$。

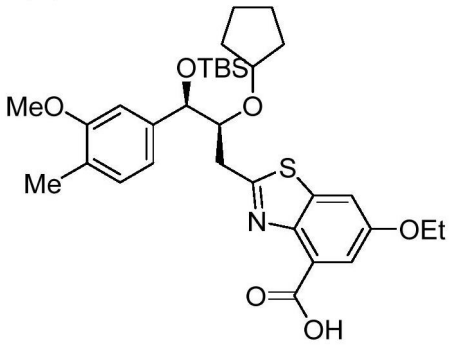
[0227] 步骤Q:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙基)-6-乙氧基苯并[d]噻唑-4-甲酸乙酯



[0228] 向(3S,4R)-4-[叔丁基(二甲基)甲硅烷基]氧基-3-(环戊基氧基)-4-(3-甲氧基-4-甲基-苯基)丁酸(300mg,709.84μmol)和2-氨基-3-[(2-氨基-5-乙氧基-3-乙氧基羰基-苯基)二硫烷基]-5-乙氧基-苯甲酸乙酯(341mg,709.84μmol)在甲苯(10mL)中的溶液中添加三丁基膦(430mg,2.13mmol)。将反应混合物在80℃下搅拌12h。将混合物用H_2O(30mL)淬

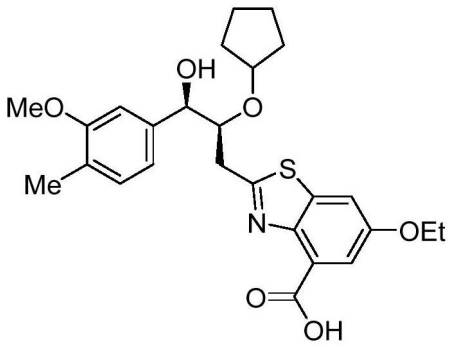
灭,用EtOAc(30mL x 3)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过硅胶柱(PE/EtOAc=10/1)纯化以得到化合物2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-甲基-苯基)丙基]-6-乙氧基-1,3-苯并噻唑-4-甲酸乙酯(110mg,产率24.7%)。LC-MS:m/z 628.3$(M+H)^+$。

[0229] 步骤R:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-甲基苯基)丙基)-6-乙氧基苯并[d]噻唑-4-甲酸



[0230] 向2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-甲基-苯基)丙基]-6-乙氧基-1,3-苯并噻唑-4-甲酸乙酯(110mg,175.19μmol)在THF(2mL)、EtOH(2mL)和H_2O(2mL)中的溶液中添加$LiOH \cdot H_2O$(37mg,875.93μmol)。将混合物在25℃下搅拌1h。将反应混合物用1N HCl调节至pH=4,用EtOAc(20mL x 3)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩以得到2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-甲基-苯基)丙基]-6-乙氧基-1,3-苯并噻唑-4-甲酸(100mg,产率95.1%),将其无需进一步纯化用于下一步骤。LC-MS:m/z 600.3$(M+H)^+$。

[0231] 步骤S:2-((2S,3R)-2-(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲基苯基)丙基)-6-乙氧基苯并[d]噻唑-4-甲酸(化合物101)

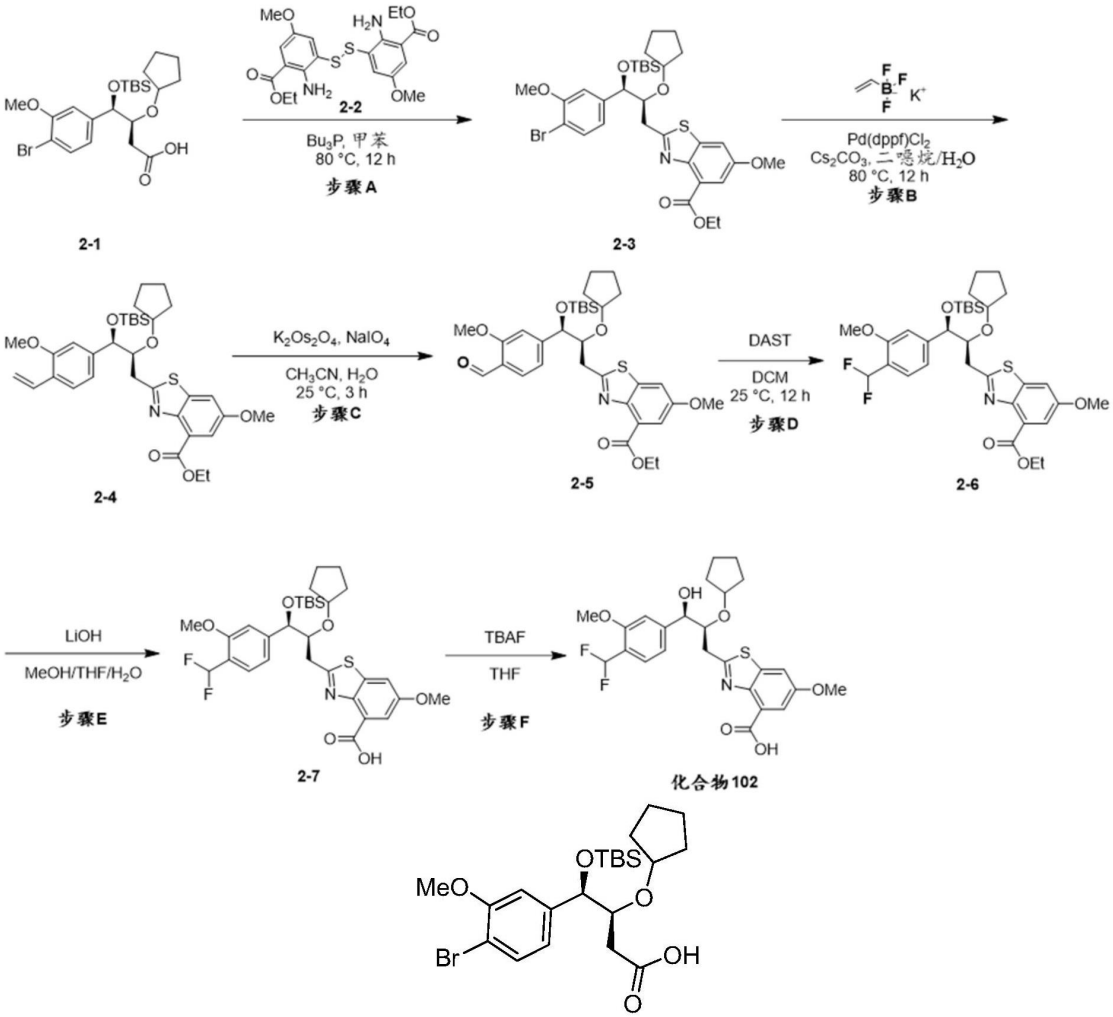


[0232] 向2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-甲基-苯基)丙基]-6-乙氧基-1,3-苯并噻唑-4-甲酸(100mg,166.71μmol)在THF(5mL)中的溶液中添加TBAF(1.67mL,1.67mmol)。将混合物在25℃下搅拌1h。将反应混合物用H_2O(30mL)稀释,用EtOAc(30mL x 3)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过制备型HPLC(柱:Welch Xtimate C18 150*30mm*5μm;流动相A:[水(0.1% HCOOH)],流动相B:CH_3CN;梯度:在7min内从55% B%到85% B%)纯化以得到2-[(2S,3R)-2-(环戊基氧基)-3-羟基-3-(3-甲氧基-4-甲基-苯基)丙基]-6-乙氧基-1,3-苯并噻唑-4-甲酸(30mg,36.5%产率)。LC-MS:m/z486.1$(M+Na)^+$。^1H NMR(400MHz,

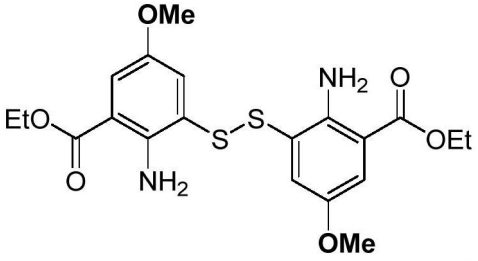
CD_3OD)δ7.74(d,J＝4.0,1H),7.71(d,J＝4.0Hz,1H),7.07(d,J＝8.0Hz,1H),6.98(s,1H),6.88(d,J＝8.0Hz,1H),4.69(d,J＝8.0Hz,1H),4.15(q,J＝8.0Hz,2H),3.98-3.88(m,2H),3.84(s,3H),3.43(d,J＝4.0Hz,2H),2.15(s,3H),1.54-1.40(m,8H),1.38-1.28(m,3H)。

实施例A2

2-((2S,3R)-2-(环戊基氧基)-3-(4-(二氟甲基)-3-甲氧基苯基)-3-羟基丙基)-6-甲氧基苯并[d]噻唑-4-甲酸(化合物102)



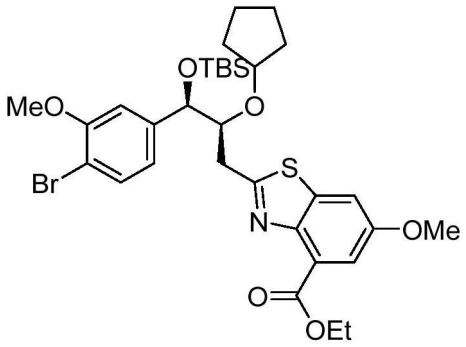
[0233] 根据对于实施例A1的制备所述的程序(在方案1中的步骤H到步骤P),通过在步骤H中使用4-溴-3-甲氧基-苯甲醛合成(3S,4R)-4-(4-溴-3-甲氧基苯基)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)丁酸(2-1)。



[0234] 根据对于实施例A1的制备所述的程序(在方案1中的步骤C至步骤D),通过在步骤C

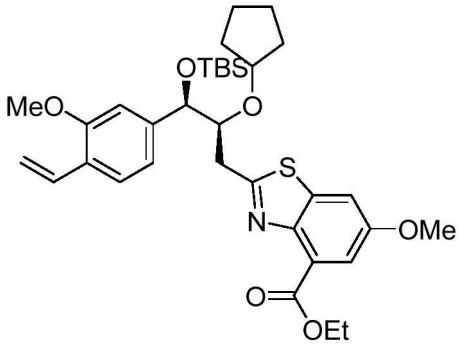
中使用2-氨基-3-溴-5-甲氧基苯甲酸甲酯合成2-氨基-3-[(2-氨基-3-乙氧基羰基-5-甲氧基-苯基)二硫烷基]-5-甲氧基-苯甲酸乙酯(2-2)。^{1}H NMR(400MHz,CDCl3)δ7.53(d,J＝3.2Hz,2H),6.88(d,J＝3.2Hz,2H),4.35(q,J＝7.2Hz,4H),3.63(s,6H),1.40(t,J＝7.2Hz,6H)。

[0235] 步骤A:2-((2S,3R)-3-(4-溴-3-甲氧基苯基)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)丙基)-6-甲氧基苯并[d]噻唑-4-甲酸乙酯



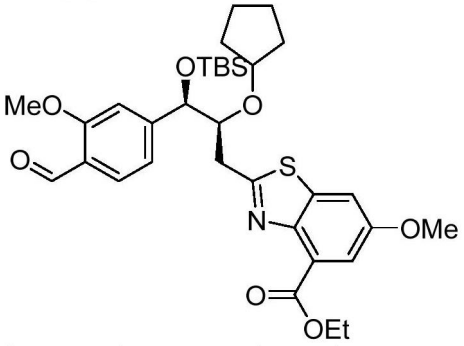
[0236] 向(3S,4R)-4-(4-溴-3-甲氧基苯基)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)丁酸(850mg,1.74mmol)和2-氨基-3-[(2-氨基-3-乙氧基羰基-苯基)二硫烷基]苯甲酸乙酯(789mg,1.74mmol)在甲苯(10mL)中的溶液中添加三丁基膦(1.06g,5.23mmol)。将反应混合物在80℃下搅拌12h。冷却后,将混合物用H_2O(30mL)淬灭,用EtOAc(30mL x 2)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过硅胶柱(PE/EtOAc＝10/1)纯化以得到呈黄色油状物的2-[(2S,3R)-3-(4-溴-3-甲氧基-苯基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)丙基]-6-甲氧基-1,3-苯并噻唑-4-甲酸乙酯(500mg,42.2%产率)。LC-MS:m/z 680.1(M+H)$^+$。

[0237] 步骤B:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3-甲氧基-4-乙烯基苯基)丙基)-6-甲氧基苯并[d]噻唑-4-甲酸乙酯



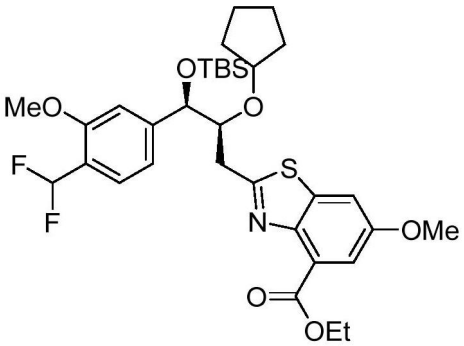
[0238] 向2-[(2S,3R)-3-(4-溴-3-甲氧基-苯基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)丙基]-6-甲氧基-1,3-苯并噻唑-4-甲酸乙酯(330mg,486.19μmol)在H_2O(2mL)和二噁烷(8mL)中的溶液中添加Pd(dppf)Cl_2(36mg,48.62μmol)、乙烯基三氟硼酸钾(130mg,972.38μmol)和Cs_2CO_3(475mg,1.46mmol)。将混合物在80℃下搅拌12h。冷却后,将混合物用H_2O(30mL)稀释,用EtOAc(30mL x 2)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过硅胶柱(PE/EtOAc＝10/1)纯化以得到2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-乙烯基-苯基)丙基]-6-甲氧基-1,3-苯并噻唑-4-甲酸乙酯(240mg,78.8%产率)。LC-MS:m/z 626.2(M+H)$^+$。

[0239] 步骤C:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(4-甲酰基-3-甲氧基苯基)丙基)-6-甲氧基苯并[d]噻唑-4-甲酸乙酯

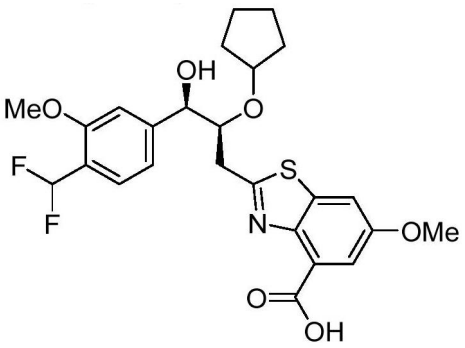


[0240] 向2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3-甲氧基-4-乙烯基-苯基)丙基]-6-甲氧基-1,3-苯并噻唑-4-甲酸乙酯(200mg,319.55μmol)在THF(3mL)和H_2O(3mL)中的溶液中添加$NaIO_4$(273mg,1.28mmol)和$K_2OsO_4.2H_2O$(1mg,1.92μmol)。将反应混合物在25℃下搅拌3h。将混合物用H_2O(30mL)淬灭,用EtOAc(30mL x 2)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过硅胶柱(PE/EtOAc=10/1)纯化以得到2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(4-甲酰基-3-甲氧基-苯基)丙基]-6-甲氧基-1,3-苯并噻唑-4-甲酸乙酯(150mg,74.7%产率)。LC-MS:m/z 628.3$(M+H)^+$。

[0241] 步骤D:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(4-(二氟甲基)-3-甲氧基苯基)丙基)-6-甲氧基苯并[d]噻唑-4-甲酸乙酯



[0242] 在0℃下向2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(4-甲酰基-3-甲氧基-苯基)丙基]-6-甲氧基-1,3-苯并噻唑-4-甲酸乙酯(150mg,238.91μmol)在DCM(3mL)中的溶液中添加DAST(192.55mg,1.19mmol)。将混合物在25℃下搅拌12h。将混合物用饱和$NaHCO_3$水溶液(30mL)淬灭,用DCM(30mL x 2)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过硅胶柱(PE/EtOAc=10/1)纯化以得到2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-[4-(二氟甲基)-3-甲氧基-苯基]丙基]-6-甲氧基-1,3-苯并噻唑-4-甲酸乙酯(70mg,45.1%产率)。LC-MS:m/z 672.2$(M+Na)^+$。

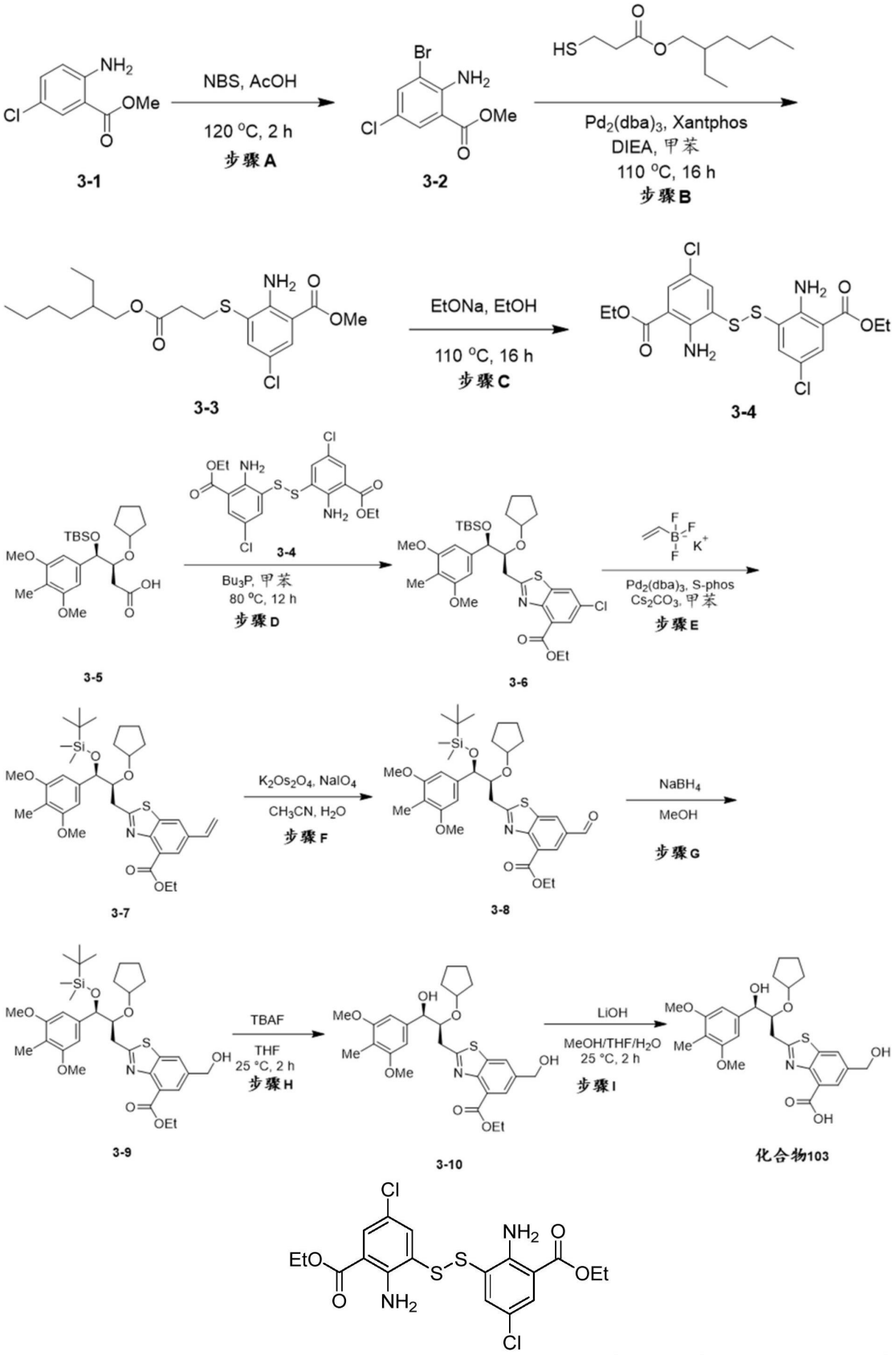


[0243] 根据对于实施例A1的制备所述的程序(在方案1中的步骤R至步骤S),通过使用2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(4-(二氟甲基)-3-甲氧基苯基)丙基)-6-甲氧基苯并[d]噻唑-4-甲酸乙酯合成2-((2S,3R)-2-(环戊基氧基)-3-(4-(二氟甲基)-3-甲氧基苯基)-3-羟基丙基)-6-甲氧基苯并[d]噻唑-4-甲酸(化合物102)。LC-MS:m/z508.0(M+H)$^+$。^{1}H NMR(400MHz,CD_3OD)δ7.75-7.72(m,1H),7.71-7.68(m,1H),7.46(d,J=8.0Hz,1H),7.16(s,1H),7.09(d,J=7.8Hz,1H),7.06-6.76(m,1H),6.92(t,J=55.6Hz,1H),4.74(d,J=4.0Hz,1H),3.99-3.93(m,2H),3.91(s,3H),3.90(s,3H),3.52-3.39(m,2H),1.58-1.45(m,3H),1.42-1.30(m,5H)。

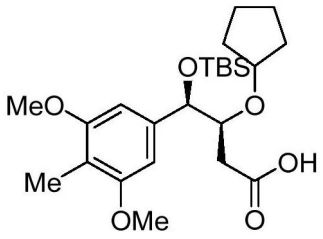
实施例A3

2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(羟基甲基)苯并[d]

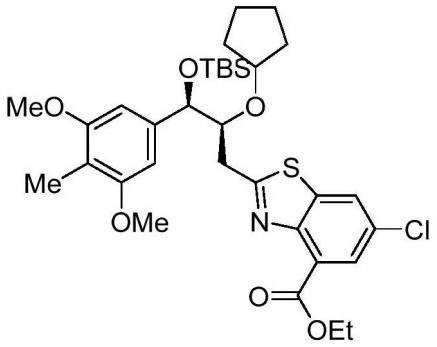
噻唑-4-甲酸(化合物103)



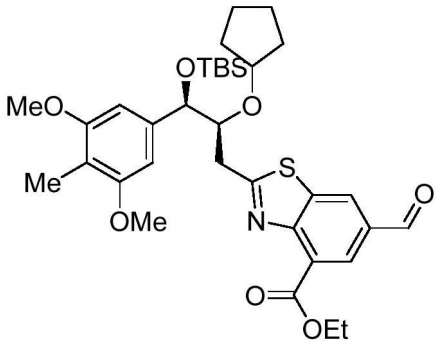
[0244] 根据对于实施例A1的制备所述的程序(在方案1中的步骤B至步骤D),通过在步骤B中使用2-氨基-5-氯-苯甲酸甲酯合成3,3'-二硫烷二基双(2-氨基-5-氯苯甲酸二乙酯)(3-4)。LC-MS:m/z 460.9$(M+H)^+$。



[0245] 根据对于实施例A1的制备所述的程序(方案1中的步骤H至步骤P),通过在步骤H中使用3,5-二甲氧基-4-甲基苯-1-甲醛合成(3S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3,5-二甲氧基-4-甲基苯基)丁酸(3-5)。^{1}H NMR(400MHz,$CDCl_3$)δ6.51(s,2H),4.71-4.70(m,1H),3.98-3.95(m,1H),3.84-3.77(m,7H),2.60-2.57(m,2H),2.06(s,3H),1.67-1.26(m,8H),0.91(s,9H),0.07(s,3H),-0.11(s,3H)。

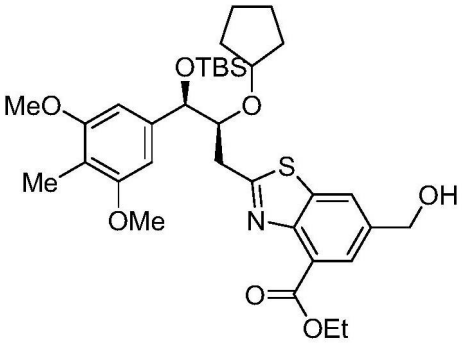


[0246] 根据对于实施例A1的制备所述的程序(在方案1中的步骤Q),通过在步骤Q中使用3,3'-二硫烷二基双(2-氨基-5-氯苯甲酸二乙酯)(3-4)和(3S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3,5-二甲氧基-4-甲基苯基)丁酸(3-5)合成2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-氯苯并[d]噻唑-4-甲酸乙酯(3-6)。^{1}H NMR(400MHz,$CDCl_3$)δ7.96-7.99(m,2H),6.55(s,2H),4.75-4.74(m,1H),4.49-4.44(m,2H),3.94-3.92(m,1H),3.83-3.82(m,7H),3.46-3.35(m,2H),2.05(s,3H),1.51-1.32(m,11H),0.91(s,9H),0.07(s,3H),-0.12(s,3H)。

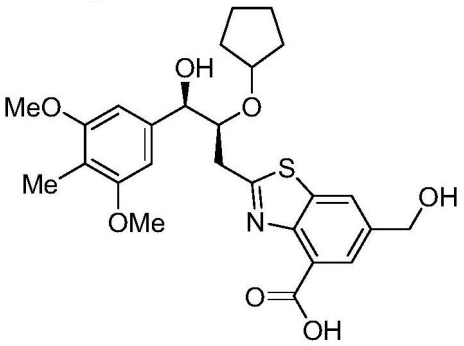


[0247] 根据对于实施例A2的制备所述的程序(在方案2中的步骤B至步骤C),通过使用2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-氯苯并[d]噻唑-4-甲酸乙酯(3-6)合成2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-甲酰基苯并[d]噻唑-4-甲酸乙酯(3-8)。LC-MS:m/z 642.2$(M+H)^+$。

[0248] 步骤G:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(羟基甲基)苯并[d]噻唑-4-甲酸乙酯



[0249] 向2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-甲酰基苯并[d]噻唑-4-甲酸乙酯(30mg,46.78μmol)在MeOH(1mL)中的溶液中添加$NaBH_4$(5.30mg,140.21μmol)。将反应混合物在25℃下搅拌3h。然后将混合物用饱和NH_4Cl水溶液(10mL)淬灭,用DCM(10mL x 3)萃取。将合并的有机层用盐水(10mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩以得到2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(羟基甲基)苯并[d]噻唑-4-甲酸乙酯(20mg,66%产率)。LC-MS:m/z 644.3$(M+H)^+$。

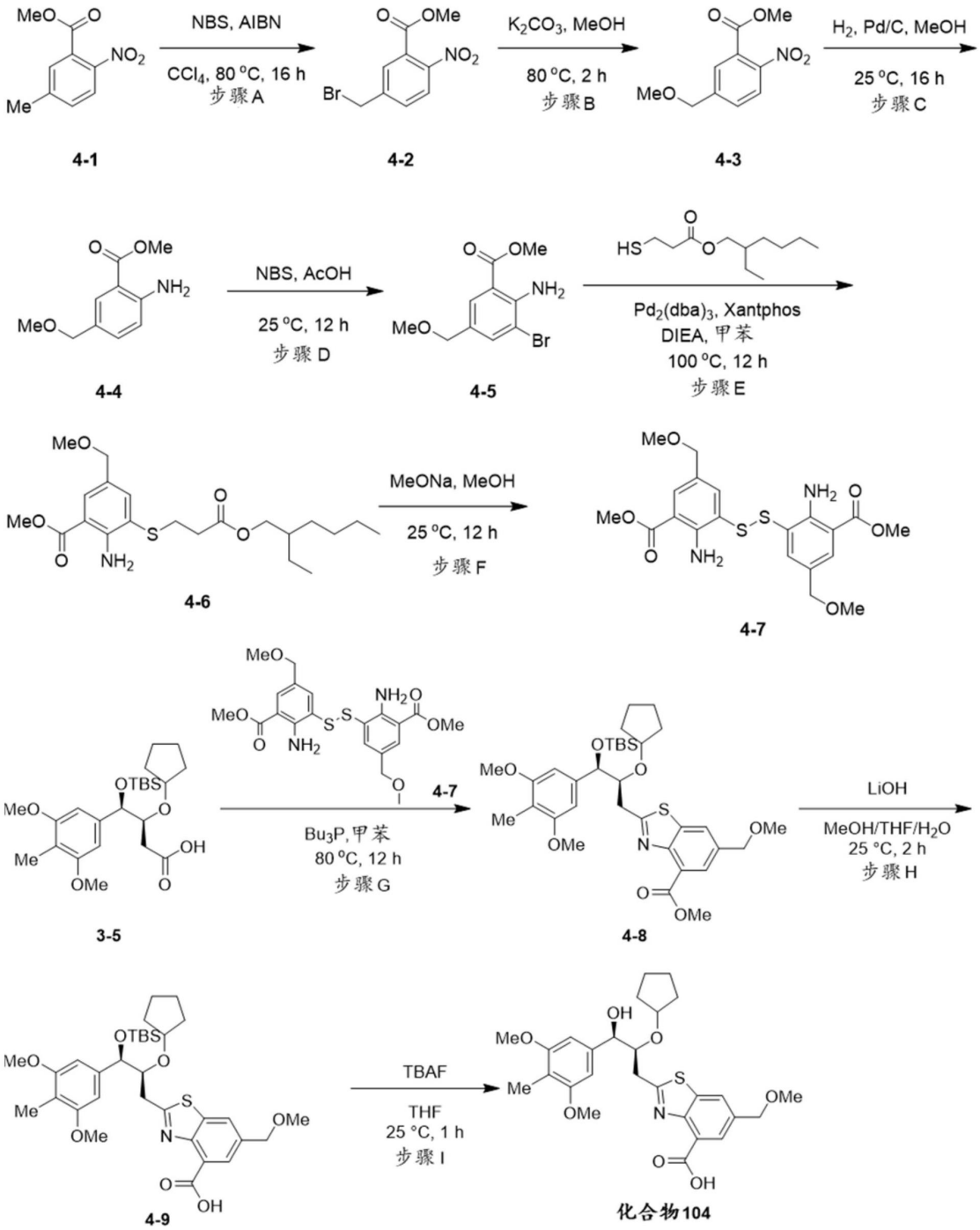


[0250] 根据对于实施例A1的制备所述的程序(在方案1中的步骤S和步骤R),通过在步骤S中使用2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(羟基甲基)苯并[d]噻唑-4-甲酸乙酯(3-9)合成2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(羟基甲基)苯并[d]噻唑-4-甲酸(化合物103)。LC-MS:m/z 502.3$(M+H)^+$。^1H NMR(400MHz,CD_3OD)δ8.05(s,1H),7.94(s,1H),6.64(s,2H),4.75(s,1H),4.61(s,2H),3.97-3.93(m,1H),3.86-3.79(m,1H),3.79(s,6H),3.45-3.43(m,2H),3.30-3.29(m,1H),1.99(s,3H),1.42-1.32(m,8H)。

实施例A4

2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(甲氧基甲基)苯并

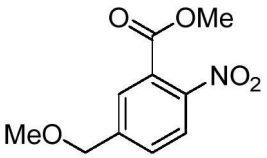
[d]噻唑-4-甲酸(化合物104)



[0251] 步骤A:5-(溴甲基)-2-硝基苯甲酸甲酯

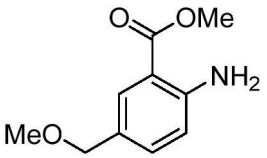
[0252] 向5-甲基-2-硝基-苯甲酸甲酯(23.5g,120.41mmol)在CCl_4(200mL)中的溶液中添加AIBN(1.98g,12.04mmol)和NBS(32.15g,180.61mmol)。将反应混合物在80℃下搅拌16h。冷却后,将反应用H_2O(300mL)稀释,用DCM(300mL x 3)萃取。将合并的有机物在减压下浓缩以得到残余物。将残余物通过柱(PE/EtOAc=7/1)纯化以得到5-(溴甲基)-2-硝基苯甲酸甲酯(19.12g,38.6%产率)。

[0253] 步骤B:5-(甲氧基甲基)-2-硝基苯甲酸甲酯

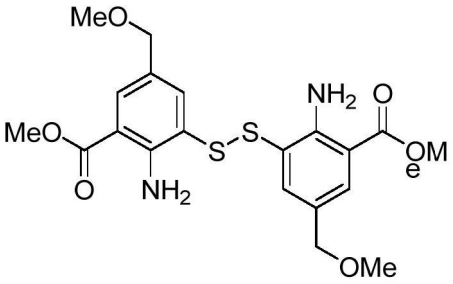


[0254] 向5-(溴甲基)-2-硝基苯甲酸甲酯(19.12g,69.77mmol)在MeOH(180mL)中的溶液中添加K_2CO_3(9.64g,69.77mmol)。将混合物在80℃下搅拌2h。将反应用H_2O(300mL)稀释,用EtOAc(300mL x 3)萃取。将合并的有机物经无水Na_2SO_4干燥,过滤并且在减压下浓缩以得到残余物。将残余物通过硅胶柱(PE/EtOAc=5/1)纯化以得到5-(甲氧基甲基)-2-硝基苯甲酸甲酯(10.52g,产率66.9%)。^1H NMR(400MHz,$CDCl_3$)δ7.85(d,J=8.4Hz,1H),7.60(d,J=1.2Hz,1H),7.51(d,J=8.4Hz,1H),4.48(s,2H),3.86(s,3H),3.38(s,3H)。

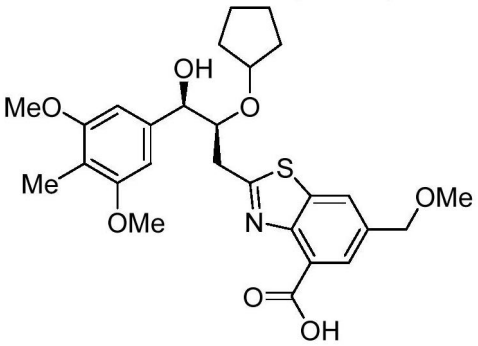
[0255] 步骤C:2-氨基-5-(甲氧基甲基)苯甲酸甲酯



[0256] 在N_2下向5-(甲氧基甲基)-2-硝基-苯甲酸甲酯(7.52g,33.39mmol)在EtOAc(100mL)中的溶液中添加10% Pd/C(2.6g),并且将混合物脱气并且用N_2吹扫3次。然后将混合物脱气并且用H_2吹扫3次。将混合物在25℃下在H_2(45psi)下搅拌16h。过滤后,将滤液在减压下浓缩以得到残余物。将残余物通过硅胶柱(PE/EtOAc=6/1)纯化以得到2-氨基-5-(甲氧基甲基)苯甲酸甲酯(5.85g,79.6%产率)。LC-MS:m/z 195.8$(M+H)^+$。



[0257] 根据对于实施例A1的制备所述的程序(在方案1中的步骤B至步骤D),通过在步骤B中使用2-氨基-5-(甲氧基甲基)苯甲酸甲酯,合成3,3'-二硫烷二基双(2-氨基-5-(甲氧基甲基)苯甲酸二甲酯)(4-7)。LC-MS:m/z 474.8$(M+Na)^+$。



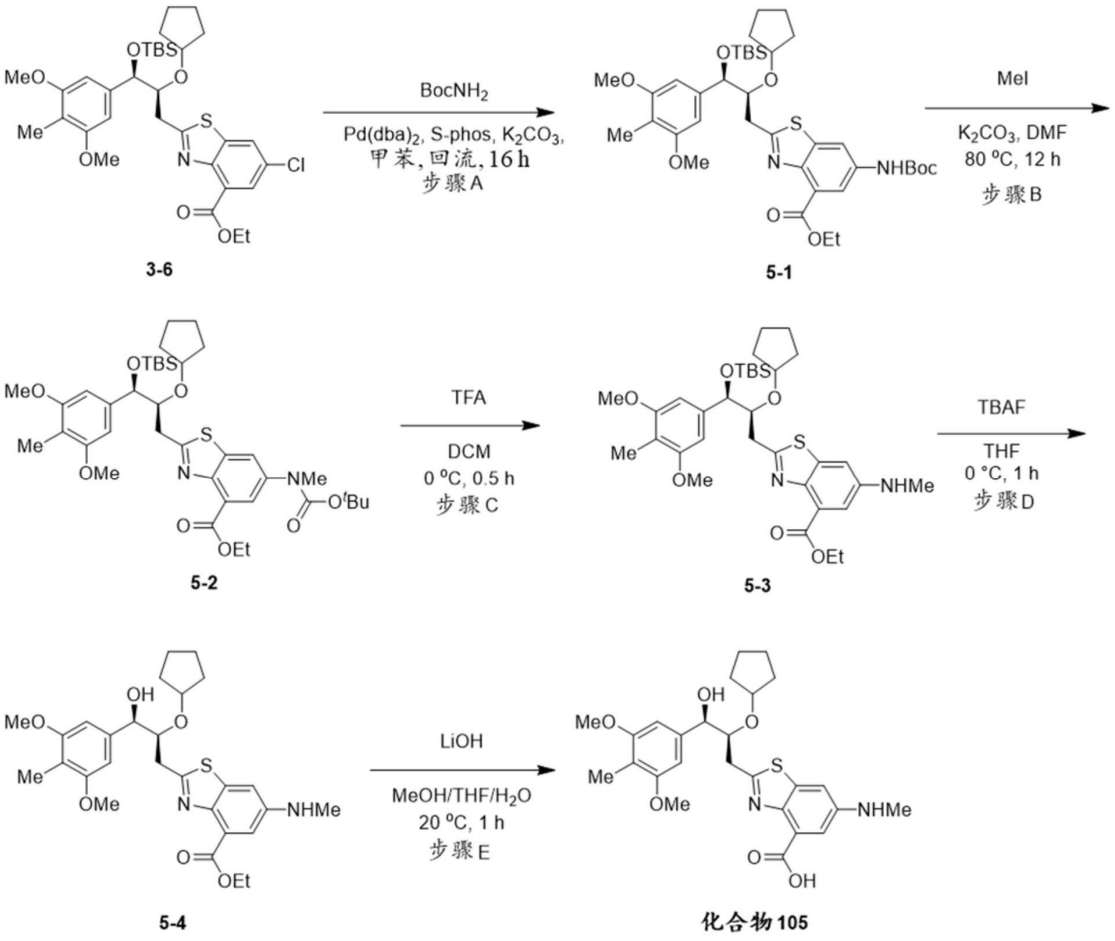
[0258] 根据对于实施例A1的制备所述的程序(在方案1中的步骤Q至步骤S),通过在步骤Q中使用3,3'-二硫烷二基双(2-氨基-5-(甲氧基甲基)苯甲酸二甲酯)(4-7)和(3S,4R)-4-

((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3,5-二甲氧基-4-甲基苯基)丁酸(3-5)合成2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(甲氧基甲基)苯并[d]噻唑-4-甲酸(化合物104)。LC-MS:m/z 516.1(M+H)$^+$。^{1}H NMR(400MHz,CD3OD)δ8.19(d,J=1.2Hz,1H),8.12(d,J=1.6Hz,1H),6.67(s,2H),4.69(d,J=5.6Hz,1H),4.65(s,2H),4.04-3.99(m,1H),3.97-3.90(m,1H),3.83(s,6H),3.53-3.48(m,2H),3.46(s,3H),1.99(s,3H),1.55-1.34(m,8H)。

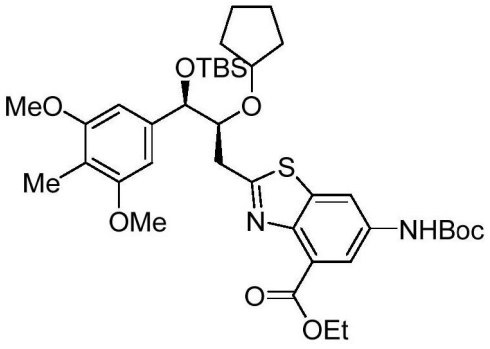
实施例A5

2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(甲基氨基)苯并[d]

噻唑-4-甲酸(化合物105)

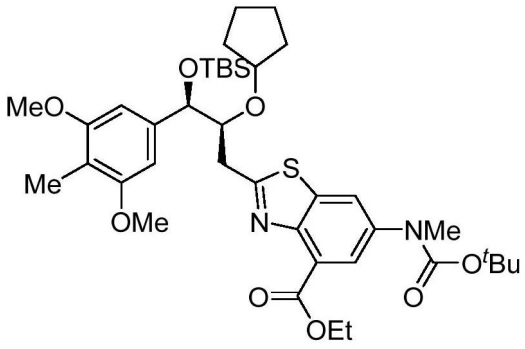


[0259] 步骤A:6-((叔丁氧基羰基)氨基)-2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)苯并[d]噻唑-4-甲酸乙酯



[0260] 向2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-6-氯-1,3-苯并噻唑-4-甲酸乙酯(500mg,771.22μmol)和氨基甲酸叔丁酯(271.04mg,2.31mmol)在甲苯(10mL)中的溶液中添加Pd(dba)$_2$(44.35mg,77.12μmol)、K_2CO_3(319.76mg,2.31mmol)和S-Phos(63.32mg,154.24μmol)。将混合物在100℃下搅拌16h。将反应混合物通过在0℃下添加H_2O(10mL)淬灭,用EtOAc(10mL x 3)萃取。将合并的有机层用盐水(10mL)洗涤,经无水Na_2SO_4干燥,过滤并且在减压下浓缩以得到残余物。将残余物通过硅胶柱(PE/EtOAc=100/1至10/1)纯化以得到6-(叔丁氧基羰基氨基)-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-1,3-苯并噻唑-4-甲酸乙酯(500mg,88.9%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ8.46(br s,1H),7.66(d,J=2.1Hz,1H),6.70(s,1H),6.56(s,2H),4.73(d,J=4.6Hz,1H),4.48-4.42(m,3H),3.95-3.90(m,1H),3.82(s,6H),3.45-3.40(m,1H),3.31-3.25(m,1H),2.06(s,3H),1.53(s,9H),1.43-1.25(m,10H),1.43-1.24(m,1H),0.91(s,9H),0.07(s,3H),-0.12(s,3H)。

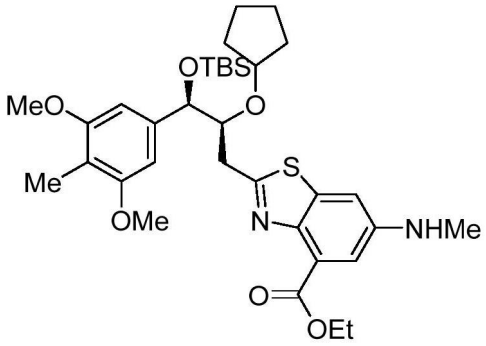
[0261] 步骤B:6-((叔丁氧基羰基)(甲基)氨基)-2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)苯并[d]噻唑-4-甲酸乙酯



[0262] 向6-(叔丁氧基羰基氨基)-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-1,3-苯并噻唑-4-甲酸乙酯(200mg,274.35μmol)在DMF(2mL)中的溶液中添加K_2CO_3(189.58mg,1.37mmol)和MeI(194.70mg,85.40μL)。将混合物在80℃下搅拌12h。冷却后,将反应混合物用H_2O(5mL)稀释,用EtOAc(5mL x 3)萃取。将合并的有机层用盐水(5mL x 3)洗涤,经无水Na_2SO_4干燥,过滤并且在减压下浓缩以得到残余物。将残余物通过制备型TLC(SiO_2,PE/EtOAc=10/1)纯化以得到6-[叔丁氧基羰基(甲基)氨基]-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-1,3-苯并噻唑-4-甲酸乙酯(40mg,19.6%产

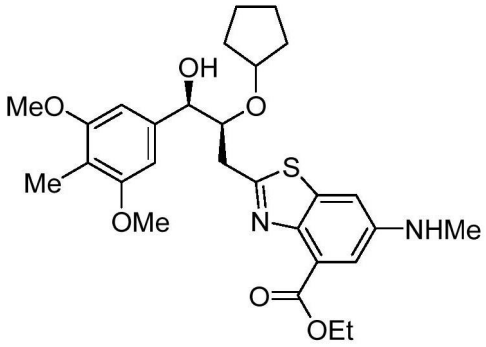
率)。LC-MS:m/z 765.3(M+Na)$^+$。

[0263] 步骤C:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(甲基氨基)苯并[d]噻唑-4-甲酸乙酯



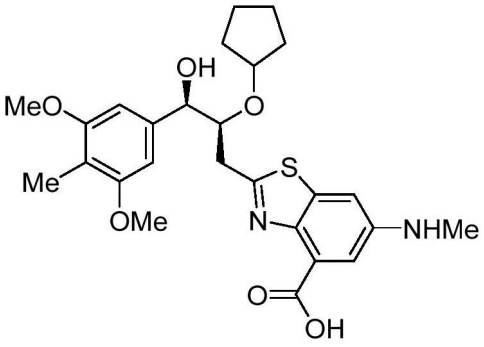
[0264] 向6-[叔丁氧基羰基(甲基)氨基]-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-1,3-苯并噻唑-4-甲酸乙酯(30mg,40.37μmol)在DCM(1mL)中的溶液中添加TFA(29.89μL,400μmol)。将反应混合物在0℃下搅拌0.5h。将反应混合物用H_2O(10mL)稀释,用EtOAc(10mL x 3)萃取。将合并的有机层用盐水(10mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩以得到2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(甲基氨基)苯并[d]噻唑-4-甲酸乙酯(22.5mg,86.7%产率),将其无需进一步纯化用于下一步骤。LC-MS:m/z 643.1(M+H)$^+$。

[0265] 步骤D:2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(甲基氨基)苯并[d]噻唑-4-甲酸乙酯



[0266] 在0℃下向2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-6-(甲基氨基)-1,3-苯并噻唑-4-甲酸乙酯(30mg,46.66μmol)在THF(0.5mL)中的溶液中添加TBAF(466.62μL,466.62μmol,在THF中的1M溶液)。将混合物在0℃下搅拌1h。将反应混合物用H_2O(10mL)稀释,并且用EtOAc(10mL x3)萃取。将合并的有机层用盐水(20mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩以得到2-[(2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)-3-羟基-丙基]-6-(甲基氨基)-1,3-苯并噻唑-4-甲酸乙酯(20mg,81.1%产率),将其无需进一步纯化用于下一步骤。LC-MS:m/z 528.7(M+H)$^+$。

[0267] 步骤E:2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(甲基氨基)苯并[d]噻唑-4-甲酸(化合物105)

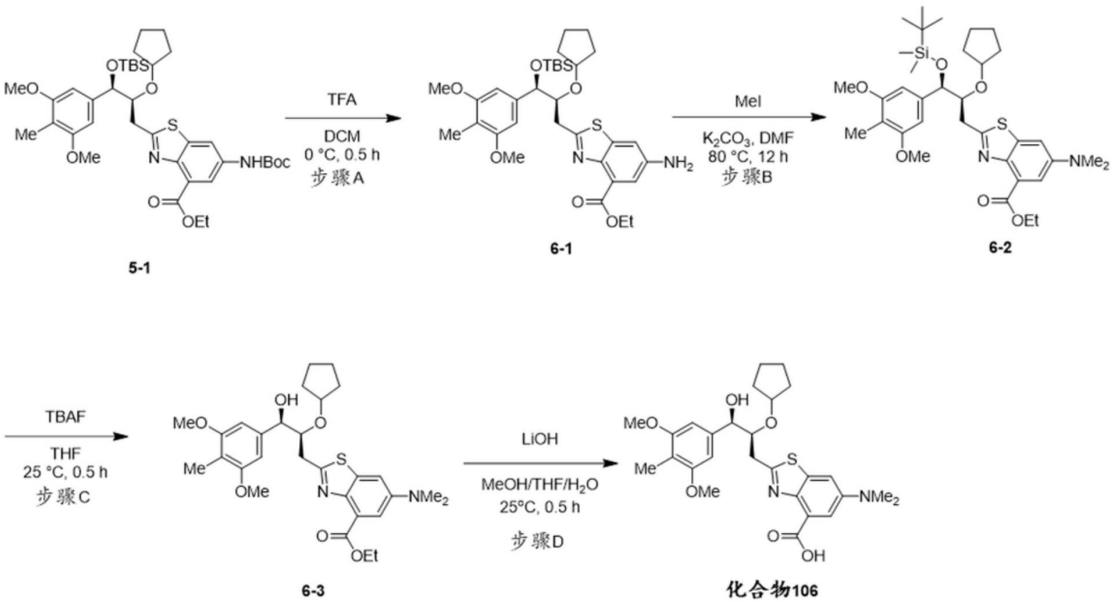


[0268] 向2-[(2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)-3-羟基-丙基]-6-(甲基氨基)-1,3-苯并噻唑-4-甲酸乙酯(20mg,37.83μmol)在THF(0.8mL)、MeOH(0.2mL)和H_2O(0.2mL)中的溶液中添加LiOH(4.53mg,189.16μmol)。将混合物在20℃下搅拌1h。将反应混合物用H_2O(10mL)稀释,用EtOAc(10mL x 3)萃取。将合并的有机层用盐水(10mL)洗涤,经无水Na_2SO_4干燥,过滤并且浓缩。将残余物通过制备型HPLC(柱:Kromasil 100-5-C18;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在10min内50% B至90% B)纯化以得到2-[(2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)-3-羟基-丙基]-6-(甲基氨基)-1,3-苯并噻唑-4-甲酸(7.92mg,产率41.8%)。LC-MS:m/z 501.3(M+H)$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ7.57(d,J=2.3Hz,1H),7.09(d,J=2.3Hz,1H),6.57(s,2H),4.93(d,J=4.3Hz,1H),4.02-3.97(m,2H),3.84(s,6H),3.31-3.24(m,1H),3.11(dd,J=3.5,15.2Hz,1H),2.92(s,3H),2.06(s,3H),1.61-1.40(m,8H)。

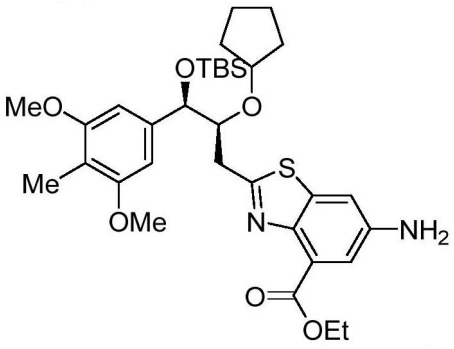
实施例A6

2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(二甲基氨基)苯并

[d]噻唑-4-甲酸(化合物106)

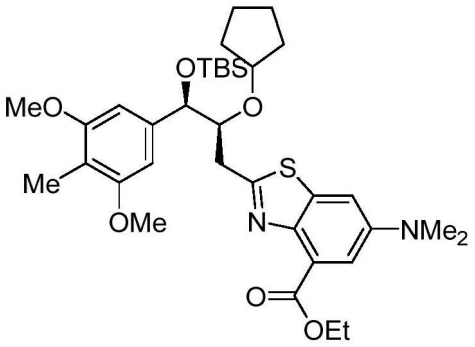


[0269] 步骤A:6-氨基-2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)苯并[d]噻唑-4-甲酸乙酯

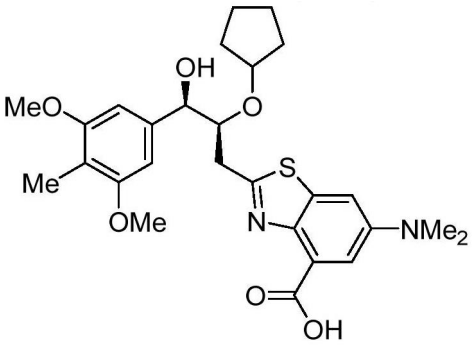


[0270] 向6-(叔丁氧基羰基氨基)-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-1,3-苯并噻唑-4-甲酸乙酯(100mg,137.17μmol)在DCM(1mL)中的溶液中添加TFA(101.56μL,1.37mmol)。将反应混合物在0℃下搅拌0.5h。将反应混合物通过添加H_2O(10mL)淬灭,用DCM(10mL x 3)萃取。将有机层经Na_2SO_4干燥,过滤并且在减压下浓缩以得到6-氨基-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-1,3-苯并噻唑-4-甲酸乙酯(80mg,92.74%产率),将其无需进一步纯化用于下一步骤。LC-MS:m/z 629.2(M+H)$^+$。

[0271] 步骤B:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(二甲基氨基)苯并[d]噻唑-4-甲酸乙酯



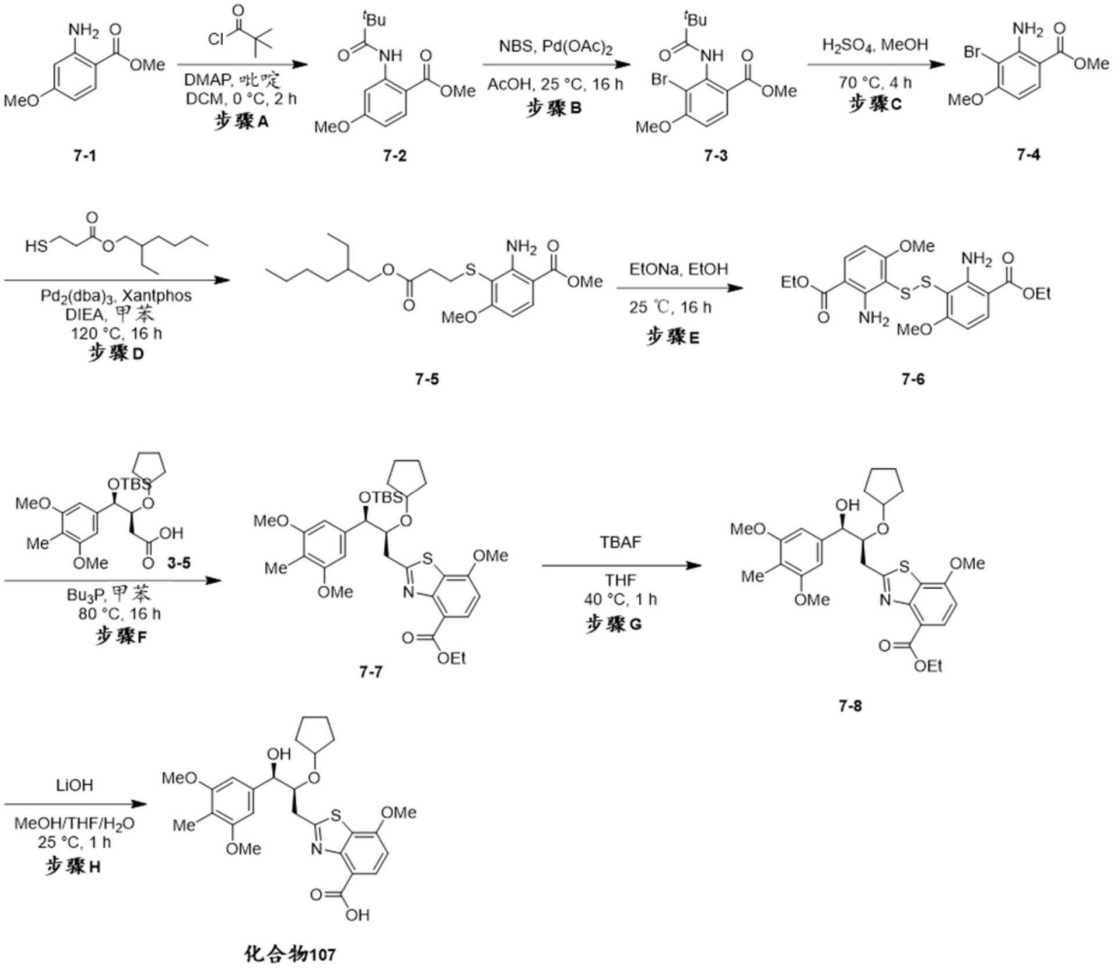
[0272] 向6-氨基-2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)苯并[d]噻唑-4-甲酸乙酯(60mg,95.41μmol)在DMF(1mL)中的溶液中添加K_2CO_3(39.56mg,286.22μmol)和MeI(23.76μL,381.62μmol)。将反应混合物在80℃下搅拌12h。冷却后,将反应混合物用H_2O(10mL)稀释,用EtOAc(10mL x 3)萃取。将合并的有机层用盐水(10mL x 3)洗涤,经Na_2SO_4干燥,过滤并且浓缩以得到2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(二甲基氨基)苯并[d]噻唑-4-甲酸乙酯(55mg,87.75%产率),将其无需进一步纯化用于下一步骤。LC-MS:m/z 657.3(M+H)$^+$。



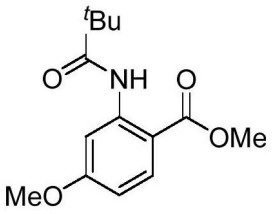
[0273] 根据对于实施例A5的制备所述的程序(在方案5中的步骤D至步骤E),通过在步骤D中使用2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-6-(二甲基氨基)苯并[d]噻唑-4-甲酸乙酯(6-2)合成2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-6-(二甲基氨基)苯并[d]噻唑-4-甲酸,实施例A6(化合物106)。LC-MS:m/z 515.3(M+H)$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ 7.73(d,J=2.7Hz,1H),7.19(d,J=2.6Hz,1H),6.58(s,2H),4.94(d,J=4.3Hz,1H),4.03-3.97(m,2H),3.85(s,6H),3.31-3.24(m,1H),3.14-3.09(m,1H),3.08(s,6H),2.07(s,3H),1.56-1.32(m,8H)。

实施例A7

2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-7-甲氧基苯并[d]噻唑-4-甲酸(化合物107)

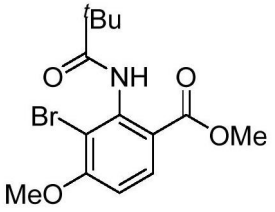


[0274] 步骤A:4-甲氧基-2-特戊酰胺基苯甲酸甲酯



[0275] 在25℃下向2-氨基-4-甲氧基苯甲酸甲酯(25g,137.98mmol)在DCM(200mL)中的溶液中添加吡啶(22.27mL,275.96mmol)和DMAP(168.57mg,1.38mmol)。然后在0℃下将2,2-二甲基丙酰氯(18.67mL,151.78mmol)逐滴添加到混合物中。将所得混合物在0℃下搅拌2h。将反应混合物用1N HCl溶液(50mL)淬灭,并且用DCM(100mL)稀释。将有机层分离,用1N HCl溶液(40mL)、饱和$NaHCO_3$水溶液(50mL)和盐水(40mL)洗涤。将有机层经无水Na_2SO_4干燥,过滤并且浓缩以得到粗4-甲氧基-2-特戊酰胺基苯甲酸甲酯(18g,60.9%产率),将其无需进一步纯化直接用于下一步骤。LC-MS:m/z 266.3$(M+H)^+$。

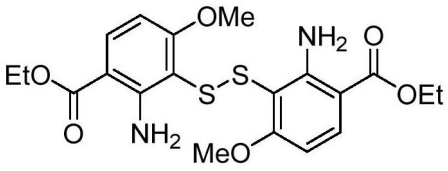
[0276] 步骤B:3-溴-4-甲氧基-2-特戊酰胺基苯甲酸甲酯



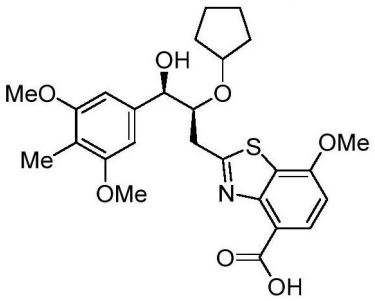
[0277] 向2-(2,2-二甲基丙酰基氨基)-4-甲氧基-苯甲酸甲酯(36g,135.69mmol)在甲苯(400mL)中的溶液中添加$Pd(OAc)_2$(6.09g,27.14mmol)、NBS(53.13g,298.53mmol)和4-甲基苯磺酸(46.73g,271.39mmol)。将反应混合物在25℃下搅拌16h。然后将反应混合物用H_2O(200mL)稀释并且过滤。将滤液用EtOAc(150mL x 3)萃取。将合并的有机层用盐水(100mL x 3)洗涤,经无水Na_2SO_4干燥,过滤并且在减压下浓缩。将残余物通过快速硅胶色谱法(ISCO®;80gSepaFlash®硅胶快速柱,在65mL/min下的0-15%EtOAc/PE梯度洗脱液)纯化以得到3-溴-2-(2,2-二甲基丙酰基氨基)-4-甲氧基-苯甲酸甲酯(4.8g,10.3%产率)。LC-MS:m/z 344.2$(M+H)^+$。

[0278] 步骤C:2-氨基-3-溴-4-甲氧基苯甲酸甲酯

[0279] 在0℃下向3-溴-4-甲氧基-2-特戊酰胺基苯甲酸甲酯(4.8g,13.95mmol)在MeOH(2mL)中的溶液中逐滴添加浓H_2SO_4(44.66g,24.27mL)。将反应混合物脱气并且用N_2吹扫3次。将所得混合物在70℃下在N_2气氛下搅拌4h。冷却后,将反应用水(50mL)稀释,用EtOAc(30mL x 3)萃取。将合并的有机层用盐水(30mL)洗涤,经无水Na_2SO_4干燥,过滤并在减压下浓缩。将残余物与PE(10mL)一起研磨,并且将悬浮液通过过滤分离。将滤饼用PE(20mL)洗涤,然后在减压下干燥以得到2-氨基-3-溴-4-甲氧基苯甲酸甲酯(2.4g,66.2%产率),将其无需进一步纯化直接用于下一步骤。LC-MS:m/z 262.1$(M+H)^+$。^1H NMR(400MHz,DMSO-d6)δ 7.82(d,J=9.0Hz,1H),6.45(d,J=9.0Hz,1H),3.87(s,3H),3.79(s,3H)。



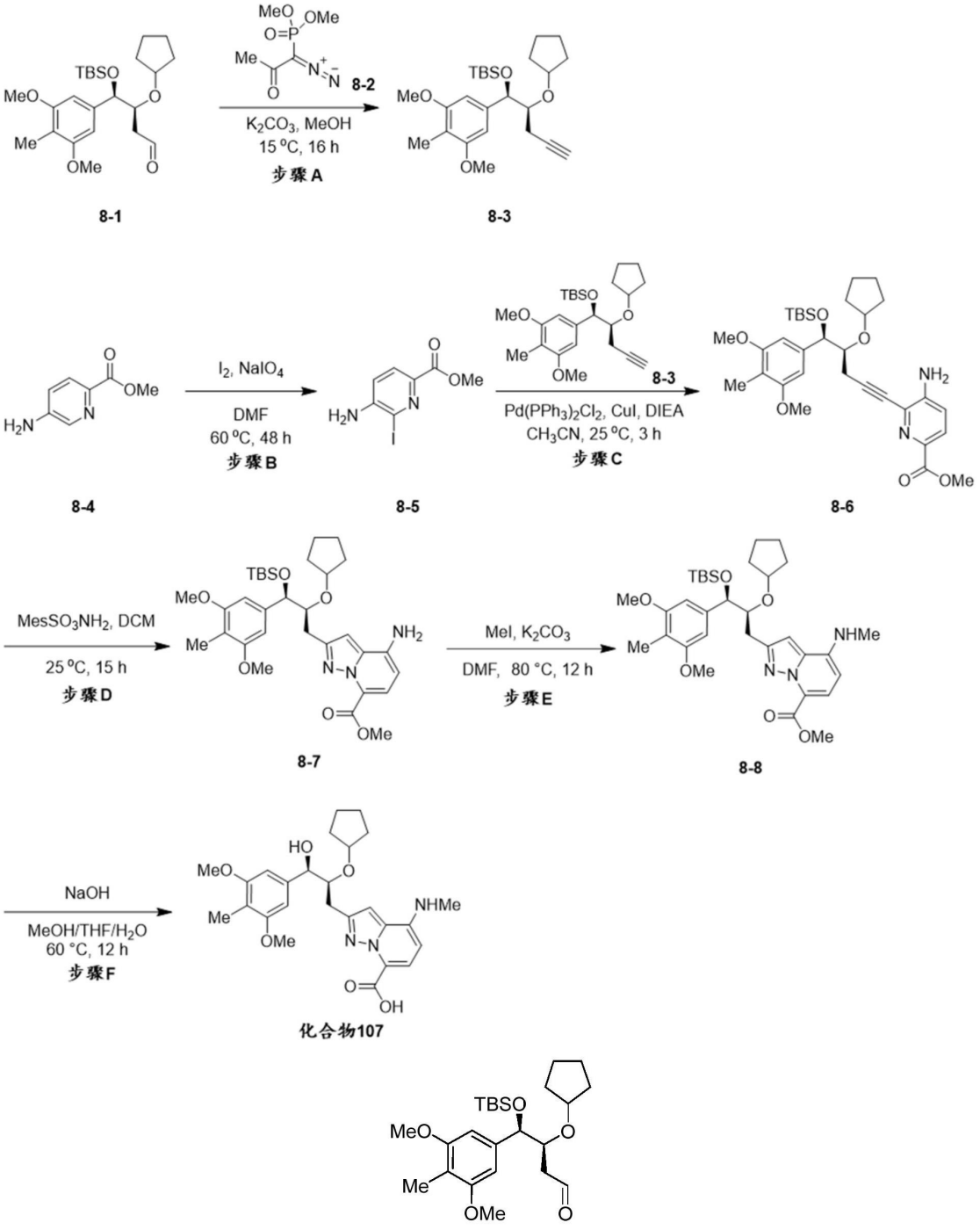
[0280] 根据对于实施例A1的制备所述的程序(在方案1中的步骤B至步骤D),通过在步骤C中使用2-氨基-3-溴-4-甲氧基苯甲酸甲酯(7-4)合成3,3'-二硫烷二基双(2-氨基-4-甲氧基苯甲酸二乙酯)(7-6)。LC-MS:m/z 474.9$(M+Na)^+$。



[0281] 根据对于实施例A1的制备所述的程序(在方案1中的步骤Q、S和R),通过在步骤D中使用3,3'-二硫烷二基双(2-氨基-4-甲氧基苯甲酸二乙酯)(7-6)合成2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-7-甲氧基苯并[d]噻唑-4-甲酸(化合物107)。LC-MS:m/z 502.3$(M+H)^+$。^{1}H NMR(400MHz,$CDCl_3$)δ13.36(brs,1H),8.32(d,J=8.6Hz,1H),6.95(d,J=8.4Hz,1H),6.58(s,2H),4.95(d,J=4.3Hz,1H),4.07(s,3H),4.06-3.98(m,2H),3.85(s,6H),3.39(dd,J=8.3,15.1Hz,1H),3.21(dd,J=3.7,15.1Hz,1H),2.06(s,3H),1.59-1.34(m,8H)。

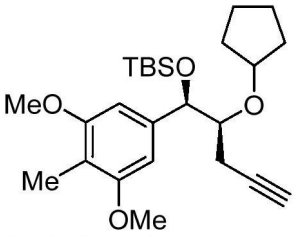
实施例A8

2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-4-(甲基氨基)吡唑并[1,5-a]吡啶-7-甲酸(化合物108)



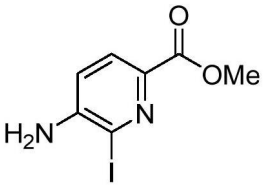
[0282] 根据对于实施例A1的制备所述的程序(在方案1中的步骤H至步骤O),通过在步骤H中使用3,5-二甲氧基-4-甲基苯-1-甲醛合成(3S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-3-(环戊基氧基)-4-(3,5-二甲氧基-4-甲基苯基)丁醛(8-1)。

[0283] 步骤A:叔丁基(((1R,2S)-2-(环戊基氧基)-1-(3,5-二甲氧基-4-甲基苯基)戊-4-炔-1-基)氧基)二甲基硅烷



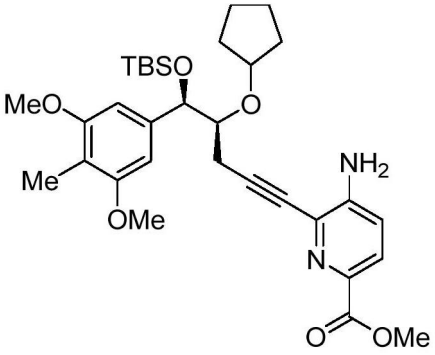
[0284] 在0℃下,将1-二唑-1-二甲氧基磷酰基-丙-2-酮(3.8g,19.8mmol)逐滴添加到(3S,4R)-4-[叔丁基(二甲基)甲硅烷基]氧基-3-(环戊基氧基)-4-(3,5-二甲氧基-4-甲基-苯基)丁醛(7.2g,16.5mmol)和K_2CO_3(4.56g,33.0mmol)在MeOH(70mL)中的混合物中。将反应混合物在15℃下在氮气下搅拌16h。将混合物在真空下浓缩。将残余物通过快速硅胶色谱法(ISCO®;220g SepaFlash®硅胶快速柱,在150mL/min下的0-4% EtOAc/PE梯度洗脱液)纯化以得到叔丁基-[(1R,2S)-2-(环戊基氧基)-1-(3,5-二甲氧基-4-甲基-苯基)戊-4-炔氧基]-二甲基硅烷(3.2g,44.9%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ6.54(s,2H),4.59-4.58(m,1H),3.85 -3.81(m,7H),3.50-3.46(m,1H),2.48-2.46(m,2H),2.07(s,3H),1.97(s,1H),1.46-1.34(m,8H),0.90(s,9H),0.07(s,3H),-0.15(s,3H)。

[0285] 步骤B:5-氨基-6-碘吡啶甲酸甲酯



[0286] 向5-氨基吡啶甲酸甲酯(10g,65.7mmol)在DMF(80mL)中的溶液中添加$NaIO_4$(5.61g,26.2mmol)和I_2(13.4g,52.7mmol。将反应混合物在60℃下搅拌48h。冷却后,向反应混合物中添加10%亚硫酸钠水溶液(100mL)。将所得混合物搅拌10分钟。通过过滤收集晶体。将收集的晶体用水洗涤,在减压下干燥以得到5-氨基-6-碘-吡啶-2-甲酸甲酯(7.84g,42.9%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.88(d,J=8.2Hz,1H),6.95(d,J=8.2Hz,1H),4.68(brs,2H),3.93(s,3H)。

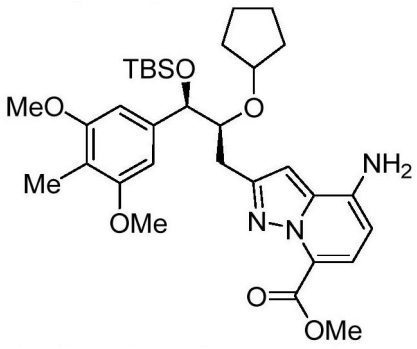
[0287] 步骤C:5-氨基-6-((4S,5R)-5-((叔丁基二甲基甲硅烷基)氧基)-4-(环戊基氧基)-5-(3,5-二甲氧基-4-甲基苯基)戊-1-炔-1-基)吡啶甲酸甲酯



[0288] 向叔丁基-[(1R,2S)-2-(环戊基氧基)-1-(3,5-二甲氧基-4-甲基-苯基)戊-4-炔氧基]-二甲基硅烷(1.71g,3.96mmol)和5-氨基-6-碘-吡啶-2-甲酸甲酯(1g,3.60mmol)在MeCN(40mL)中的溶液中添加$Pd(PPh_3)_2Cl_2$(252mg,360μmol)、CuI(68.5mg,360μmol)和DIEA

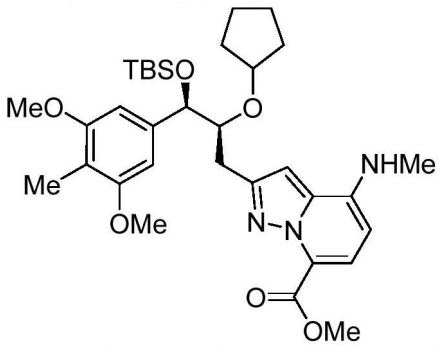
(3.13mL,17.95mmol)。将所得混合物在25℃下搅拌3h。将混合物用水(200mL)稀释,用EtOAc(150mL x 3)萃取。将合并的有机相经无水Na_2SO_4干燥,过滤并且浓缩以得到残余物。将残余物通过快速硅胶色谱法(ISCO®;40g SepaFlash®硅胶快速柱,在100mL/min下的0-20%EtOAc/PE梯度洗脱液)纯化以得到5-氨基-6-[(4S,5R)-5-[叔丁基(二甲基)甲硅烷基]氧基-4-(环戊基氧基)-5-(3,5-二甲氧基-4-甲基-苯基)戊-1-炔基]吡啶-2-甲酸甲酯(1.77g,84.2%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.88(d,J=8.6Hz,1H),6.99(d,J=8.6Hz,1H),6.55(s,2H),4.75(s,2H),4.65(d,J=6.0Hz,1H),3.93(s,3H),3.87(d,J=2.8Hz,1H),3.83(s,6H),3.66-3.57(m,1H),2.91-2.81(m,1H),2.80-2.70(m,1H),2.08(s,3H),1.73-1.63(m,2H),1.52-1.30(m,6H),0.91(s,9H),0.08(s,3H),-0.13(s,3H)。

[0289] 步骤D:4-氨基-2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)吡唑并[1,5-a]吡啶-7-甲酸甲酯



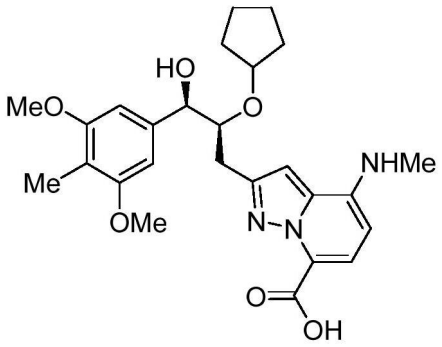
[0290] 将((均三甲苯基磺酰基)氧基)氨基甲酸叔丁酯(946mg,3mmol)和TFA(5mL)的混合物在0℃下搅拌1h。将混合物倒入冰冷的水(150mL)中,用DCM(20mL x 2)萃取。在25℃下将合并的有机层经无水Na_2SO_4干燥、过滤并且将滤液逐滴添加到5-氨基-6-[(4S,5R)-5-[叔丁基(二甲基)甲硅烷基]氧基-4-(环戊基氧基)-5-(3,5-二甲氧基-4-甲基-苯基)戊-1-炔基]吡啶-2-甲酸甲酯(0.96g,1.65mmol)在DCM(20mL)中的溶液中。将所得混合物在25℃下搅拌15h。将反应混合物用饱和$NaHCO_3$水溶液(150mL)淬灭。将有机层分离,经无水Na_2SO_4干燥,过滤并且浓缩以得到残余物。将残余物通过快速硅胶色谱法(ISCO®;20g SepaFlash®硅胶快速柱,在80mL/min下的0-20%-40% EtOAc/PE梯度洗脱液)纯化以得到4-氨基-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]吡唑并[1,5-a]吡啶-7-甲酸甲酯(168mg,17.1%产率)。LC-MS:m/z 598.8$(M+H)^+$。

[0291] 步骤E:2-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)丙基)-4-(甲基氨基)吡唑并[1,5-a]吡啶-7-甲酸甲酯



[0292] 向4-氨基-2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]吡唑并[1,5-a]吡啶-7-甲酸甲酯(84mg,141μmol)在DMF(2mL)中的溶液中添加K_2CO_3(58.3mg,422μmol)和MeI(70.0μL,1.12mmol)。将反应混合物在80℃下搅拌12h。冷却后,将混合物用水(30mL)稀释,用EtOAc(30mL x 4)萃取。将合并的有机层经无水Na_2SO_4干燥,过滤并且浓缩以得到残余物。将残余物通过快速硅胶色谱法(ISCO®;4g SepaFlash®硅胶快速柱,在100mL/min下的0-20% EtOAc/PE梯度洗脱液)纯化以得到2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-4-(甲基氨基)吡唑并[1,5-a]吡啶-7-甲酸甲酯(20mg,23.3%产率)。LC-MS:m/z 634.0$(M+Na)^+$。

[0293] 步骤F:2-((2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基苯基)-3-羟基丙基)-4-(甲基氨基)吡唑并[1,5-a]吡啶-7-甲酸



[0294] 向2-[(2S,3R)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)丙基]-4-(甲基氨基)吡唑并[1,5-a]吡啶-7-甲酸甲酯(20mg,32.7μmol)在THF(2mL)、MeOH(5mL)和H_2O(2mL)中的溶液中添加NaOH(261mg,6.54mmol)。将反应混合物在60℃下搅拌12h。在真空下去除溶剂。将残余物用水(5mL)稀释,用6N HCl酸化至pH=4-5。将混合物用EtOAc(30mL x 3)萃取。将有机层经Na_2SO_4干燥,过滤并且在真空下浓缩以得到残余物。将残余物通过制备型HPLC(柱:Kromasil100-5-C18;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在8min内50% B至80% B)纯化以得到2-[(2S,3R)-2-(环戊基氧基)-3-(3,5-二甲氧基-4-甲基-苯基)-3-羟基-丙基]-4-(甲基氨基)吡唑并[1,5-a]吡啶-7-甲酸(2.33mg,14.52%产率)。LC-MS:m/z 484.3$(M+H)^+$。^{1}H NMR(400MHz,CD_3OD)δ7.76(d,J=8.2Hz,1H),6.71(s,1H),6.64(s,2H),6.24(d,J=8.2Hz,1H),4.61-4.58(m,2H),3.87-3.74(m,8H),3.22-3.14(m,1H),3.07-3.01(m,1H),3.00(s,3H),1.99(s,3H),1.46-1.24(m,8H)。

[0295] 表1中的化合物可以或已经使用上述实施例中所述的类似程序使用合适的起始材料合成。某些化合物的数据如下表所示。某些化合物的纯化条件如下。

[0296] 化合物102的制备型HPLC分离条件:色谱柱:Welch Xtimate C18 150*30mm*5μm;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在7min内57% B至87%B。

[0297] 化合物103的制备型HPLC分离条件:色谱柱:Kromasil 100-5-C18;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在10min内50% B至80% B。

[0298] 化合物104的制备型HPLC分离条件:色谱柱:Welch Xtimate C18 150*30mm*5μm;流动相A:水(0.01% NH_3H_2O+10mM NH_4HCO_3),流动相B:CH_3CN;梯度:在9min内20% B至50%

B。

[0299] 化合物106的制备型HPLC分离条件:色谱柱:Kromasil 100-5-C18;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在10min内50% B至90% B。

[0300] 化合物107的制备型HPLC分离条件:色谱柱:Kromasil 100-5-C18;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在10min内50% B至85% B。

[0301] 化合物109的制备型HPLC分离条件:色谱柱:Kromasil 100-5-C18;流动相A:水(0.1% CF3COOH),流动相B:CH_3CN;梯度:在10min内50% B至90% B。

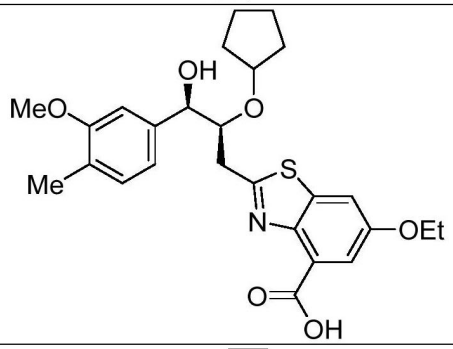
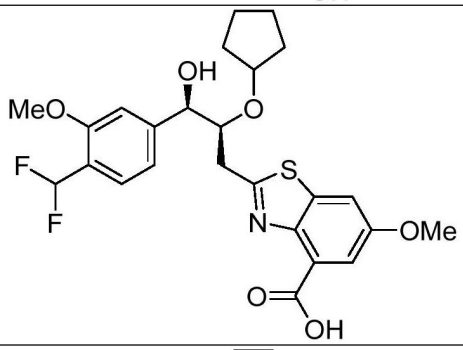
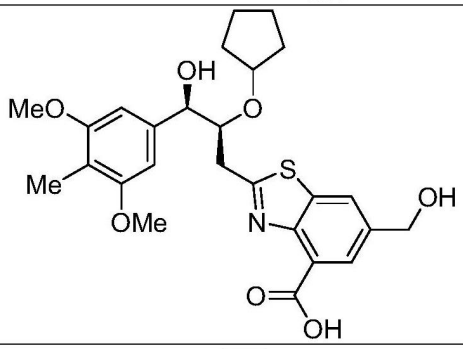
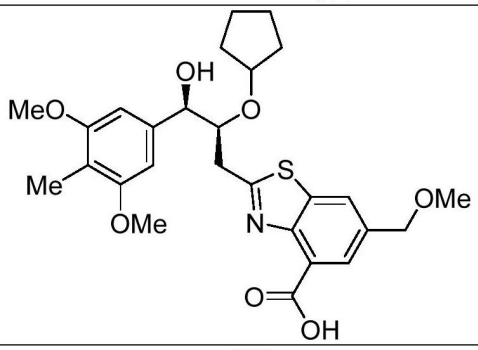
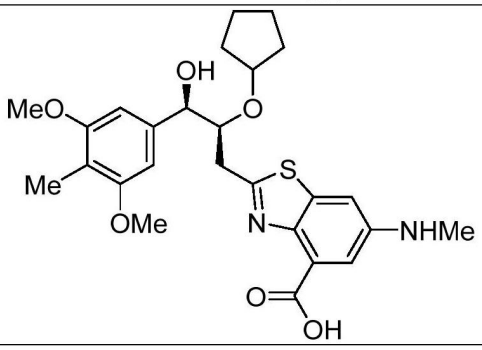
[0302] 化合物110的制备型HPLC分离条件:色谱柱:Kromasil 100-5-C18;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在9min内55% B至95% B。

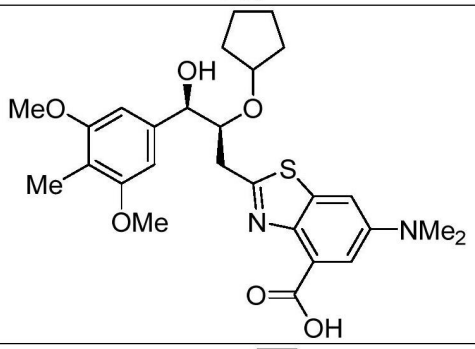
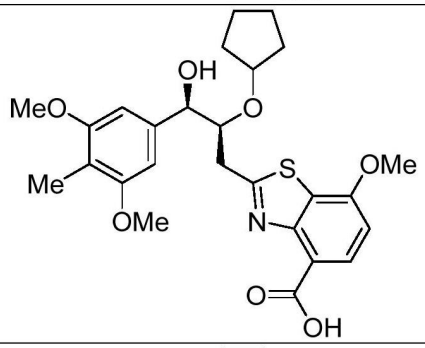
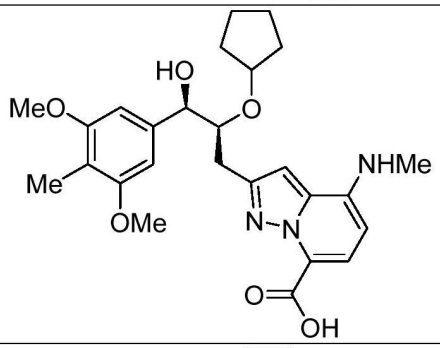
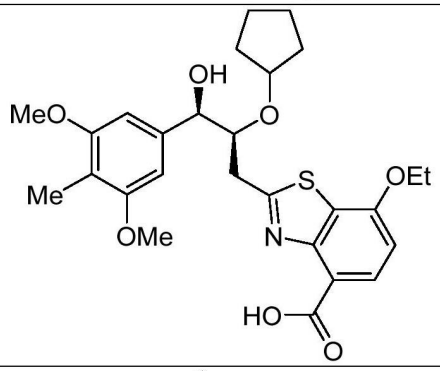
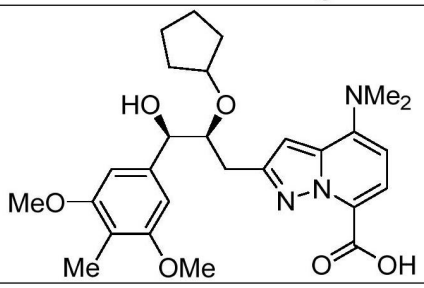
[0303] 化合物111的制备型HPLC分离条件:色谱柱:Boston Green ODS(150*30mm*5μm);流动相A:水(0.225% HCOOH),流动相B:CH_3CN;梯度:在8min内60% B至90% B。

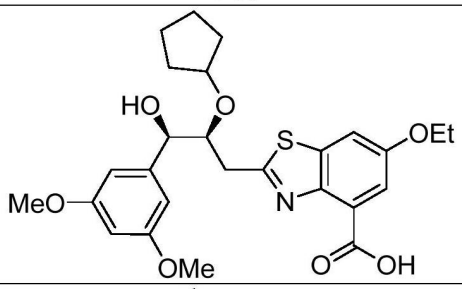
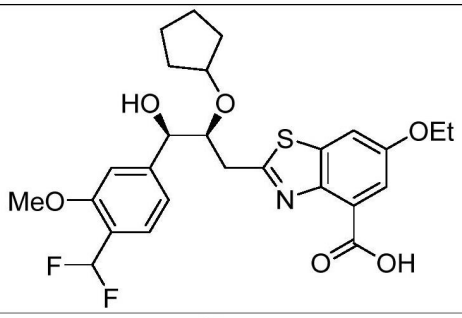
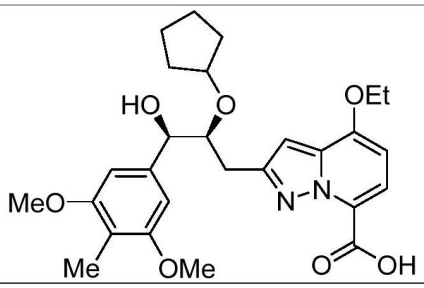
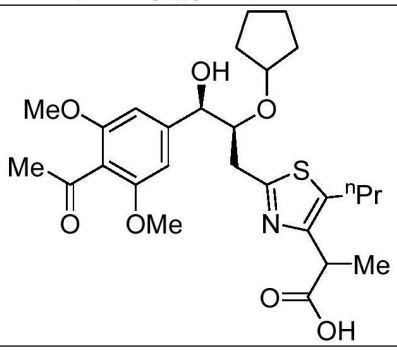
[0304] 化合物112的制备型HPLC分离条件:色谱柱:Phenomenex Gemini-NX C18 75*30mm*3μm;流动相A:水(0.225% HCOOH),流动相B:CH_3CN;梯度:在8min内63%B至93% B。

[0305] 化合物113的制备型HPLC分离条件:色谱柱:Kromasil 100-5-C18;流动相A:水(0.1% HCOOH),流动相B:CH_3CN;梯度:在10min内55% B至100% B。

[0306] 化合物114的制备型HPLC分离条件:色谱柱:DAICEL CHIRALPAK IF(250mm*30mm*10μm);流动相A:水(0.1% NH_3H_2O),流动相B:EtOH;梯度:在8min内20% B至20% B。

化合物	结构	LC-MS：m/z
101		486.1 $(M+H)^+$
102		508.0 $(M+H)^+$
103		502.3 $(M+H)^+$
104		538.1 $(M+Na)^+$
105		501.3 $(M+H)^+$

化合物	结构	LC-MS：m/z
106		515.3 $(M+H)^+$
107		502.3 $(M+H)^+$
108		484.3 $(M+H)^+$
109		516.4 $(M+H)^+$
110		498.4 $(M+H)^+$

化合物	结构	LC-MS：m/z
111		502.1 $(M+H)^+$
112		522.0 $(M+H)^+$
113		499.4 $(M+H)^+$
114		520.0 $(M+H)^+$

生物学测定

体外LPA1功能拮抗剂测定

[0307] 在测试之前,将过表达人LPA1的CHO-K1细胞以总体积20μL接种到黑壁、透明底、多聚-D-赖氨酸包被的384孔微板上并且在37℃下孵育适当时间。在由在HBSS/20mM Hepes中的1x染料、1x添加剂A和2.5mM丙磺舒组成的1x染料加载缓冲液中进行测定。丙磺舒是新鲜制备的。在测试之前,将细胞与染料一起加载。从细胞抽出培养基并且用20μL染料加载缓冲液替代。将细胞在37℃下孵育30-60分钟。染料加载后,将细胞从培养箱中取出并且添加10μL 3X测试化合物。将细胞在室温下在黑暗中孵育30分钟以平衡板温度,然后进行0.018μM的油酰基LPA激发。在FLIPR Tetra(MDS)上测量化合物拮抗剂活性。监测钙动员2分钟并且测定5秒后将10μL在HBSS/20mM Hepes中的油酰基LPA添加到细胞。使用CBIS数据分析套件(ChemInnovation,加利福尼亚州)分析化合物活性。使用以下公式计算百分比抑制:

抑制%＝100%x(1-(测试样品的平均RFU-媒介物对照的平均RFU)/(LPA对照的平

均RFU-媒介物对照的平均RFU))。

体外LPA1钙通量拮抗剂测定

[0308] 将过表达人LPA1和G15a的CHO-K1细胞以总体积20μL(15000个细胞/孔)接种到基质胶预包被的384孔板(corning-3764)中并且在37℃下孵育。孵育过夜后,将细胞血清饥饿4h。在含有在HBSS/20mM Hepes中的1x Fluo-8 AM(AAT Bioquest,21080)和2.5mM丙磺舒(Thermo Fisher,36400)的染料加载缓冲液中进行测定。细胞饥饿后,用20μL染料加载缓冲液代替培养基,并且在37℃下孵育30min。然后将5μL在染料加载缓冲液中滴定的5X化合物添加到细胞,并且孵育30min,随后在EC80下通过LPA进行激发。在FLIPR Tetra(MDS)上测量钙动员。对于LPA EC80测定,将饥饿的细胞与20μL染料加载缓冲液一起孵育1h,然后将5μL在染料加载缓冲液中滴定的5X化合物添加到细胞。在FLIPR上监测由LPA诱导的钙信号。

[0309] 使用以下公式计算百分比抑制:

抑制%=100%x(1-(测试样品的平均RFU-DMSO的平均RFU)/(LPA对照的平均RFU-DMSO的平均RFU))。

[0310] 表B1示出了在体外LPA1钙离子通量拮抗剂测定中化合物的生物活性。测试化合物的活性提供于下表B1中,如下:+++=IC_{50}<10nM;++=IC_{50} 10nM-100nM;+=IC_{50}>100nM。

表B1

化合物	活性
101	+++
102	+++
103	++
104	+++
105	+++

化合物	活性
106	+++
107	+++
108	++
109	+++
110	+

化合物	活性
111	++
112	++
113	++
114	++

体内研究

在小鼠中的药代动力学测量

[0311] 在单次口服(5mg/kg)施用后,在CD1雌性小鼠中测量所选化合物的PK特性。

[0312] 将化合物103和104分别以1mg/mL在10% Solutol HS15和90%生理盐水的溶液中制备,以用于以5mL/kg口服施用,并且被施用于3只小鼠/3组。给药后,在0.25、0.5、1、2、4、6、8、24h通过跖背静脉取样进行血液采集,随后离心以获得血浆。在化合物萃取和LC-MS/MS分析之前,样品在-80℃下冷冻保存。在小鼠中的化合物103和104药代动力学参数通过标准非房室模型从全身血浆浓度-时间曲线计算。

[0313] 表B2示出了通过非房室模型确定的化合物103和104在小鼠(CD1;雌性)中的平均药代动力学参数。

表B2

PK参数	化合物	
	103	104
T_{max} (h)	0.500	0.250
C_{max} (ng/mL)	463	3837
$AUC_{最后}$ (h*ng/mL)	1643	6947

在大鼠中的药代动力学测量

[0314] 在SD雄性大鼠中在单次口服(5mg/kg)和静脉内施用(1mg/kg)后测量所选化合物的PK特性。

[0315] 将化合物103和104分别以1mg/mL在10％ Solutol HS15和90％生理盐水的溶液中制备,以用于以5mL/kg口服施用;以及以0.2mg/mL在10％ Solutol HS15和90％生理盐水的溶液中制备,以用于以1mL/kg静脉内施用,并且施用于每组3只大鼠。给药后,分别在0.25、0.5、1、2、4、6、8、24h以及在0.083、0.25、0.5,1、2,4、8、24h,通过颈静脉取样(通过插管)进行血液采集,随后离心以获得血浆。在化合物萃取和LC-MS/MS分析之前,样品在-80℃下冷冻保存。在大鼠中的化合物103和104的药代动力学参数通过标准非房室模型从全身血浆浓度-时间曲线计算。

[0316] 表B3示出了通过非房室模型确定的化合物103和104在大鼠(SD;雄性)中的平均药代动力学参数。

表B3

PK参数	化合物			
	103		104	
途径	IV	PO	IV	PO
Cl观测值（mL/min/kg）	12.9	ND	8.8	ND
T_{max}（h）	ND	0.25	ND	0.25
C_{max}（ng/mL）	ND	1493	ND	1519
$AUC_{最后}$（h*ng/mL）	1334	1794	1899	2894
F（%）	ND	27.3	ND	30.3