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(54) **HETEROCYCLIC COMPOUNDS USEFUL IN THE TREATMENT OF DISEASE**

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(57) **ABSTRACT**

Heterocyclic compounds are described that are lysophosphatidic acid receptor ligands that are useful in the treatment of lysophosphatidic acid receptor-dependent diseases and conditions.

# HETEROCYCLIC COMPOUNDS USEFUL IN THE TREATMENT OF DISEASE

## STATEMENT OF GOVERNMENT INTEREST

**[0001]** This invention was made with government support under Grant DK092005 awarded by the National Institutes of Health. The US government has certain rights in the invention.

## CROSS REFERENCE TO RELATED APPLICATIONS

**[0002]** This application claims the benefit of U.S. patent application Ser. No. 16/010,755, filed Jun. 18, 2018, the entire contents of which is hereby incorporated by reference herein.

## FIELD OF THE INVENTION

**[0003]** The present invention relates to compounds having pharmacological activity, to processes for preparation of such compounds, to pharmaceutical compositions comprising them, and to their use in therapy and prophylaxis of disease in a subject in need thereof, in particular for human and veterinarian treatments of pain, pruritus, cancer, inflammation and fibrotic diseases.

## BACKGROUND OF THE INVENTION

**[0004]** Lysophospholipids affect fundamental cellular functions that include proliferation, differentiation, survival, migration, adhesion, invasion, and morphogensis. Abnormal functions influence many biological processes leading to disease that include, but are not limited to fibrotic disease, inflammation, cancer and peripheral nerve injury. Lysophosphatidic acid (LPA) is a lysophospholipid that has been shown to act through specific G protein-coupled receptors (GPCRs) in an autocrine and paracrine fashion. Antagonists of the LPA receptors find use in the treatment of diseases, disorders or conditions in which LPA plays a role.

**[0005]** Agents that interact with the lysophosphatidic acid receptors [LPARs] to reduce signal transduction through those receptors (i.e., by competitive or noncompetitive inhibition or acting as inverse agonists) reduce manifestations of the diseases described herein. Diseases and conditions whose etiology, progression or persistence is effected by in whole or in part by signaling through the lysophosphatidic acid receptor subtype 1 (LPA1R) are considered LPA-dependent. New agents having therapeutic utility for treating those LPA-dependent and other conditions and diseases described herein are needed.

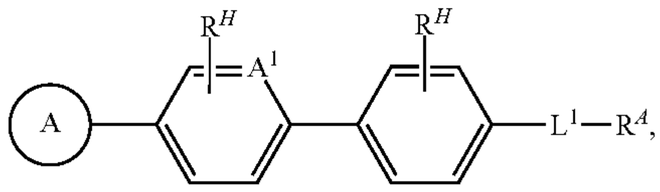
## SUMMARY OF THE INVENTION

**[0006]** Disclosed herein are compounds that inhibit the physiological activity of lysophosphatidic acid (LPA), and therefore, are useful as agents for the treatment or prevention of diseases in which inhibition of the physiological activity of LPA is useful.

**[0007]** In one aspect, those compounds are useful for the treatment of fibrosis of organs (e.g., liver, kidney, lung, heart and the like), liver diseases (e.g., acute hepatatis, chronic hepatitis, liver fibrosis, liver cirrhosis, portal hypertension, regenerative failure, nonalcoholic steatohepatitis (NASH), liver hypofunction, hepatic blood flow disorder, and the like), cell proliferative disease such as cancers (including but not limited to solid tumor, solid tumor metastasis, vascular fibroma, myeloma, multiple myeloma, Kaposi's sarcoma, leukemia, chronic lymphocytic leukemia (CLL), invasive metastasis of cancer cell, and the like), inflammatory diseases (including but not limited to psoriasis, nephropathy, pneumonia and the like), gastrointestinal tract disease (including but not limited to (irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), abnormal pancreatic secretion, and the like), renal disease, urinary tract-associated disease (including but not limited to 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 (including but not limited to obstruction of lower urinary tract, and the like), inflammatory disease of lower urinary tract, (including but not limited to dysuria, frequent urination, and the like), pancreas disease, abnormal angiogenesis-associated disease (including but not limited to arterial obstruction and the like), scleroderma, brain-associated disease (including but not limited to cerebral infarction, cerebral hemorrhage, and the like), nervous system diseases (including but not limited to neuropathic pain, peripheral neuropathy, pruritus and the like), ocular disease (including but not limited to age-related macular degeneration (AMD), diabetic retinopathy, proliferative vitreo-retinopathy (PVR), cicatricial pemphigoid, glaucoma filtration surgery scarring, and the like).

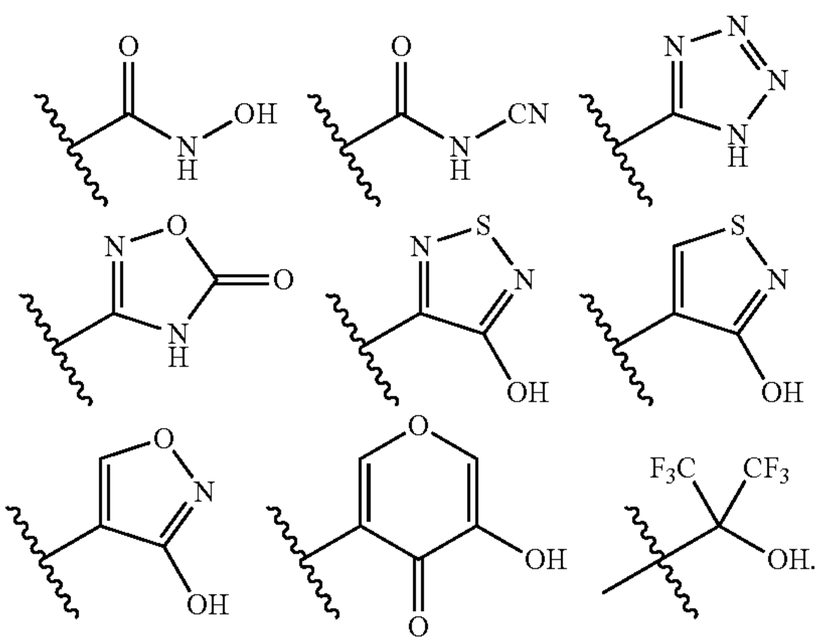
**[0008]** The compounds of the invention include compounds of Formula I that have the structure:

Formula I

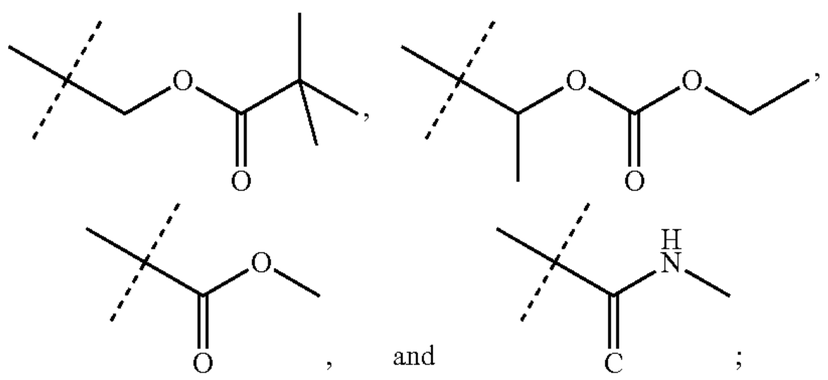



or a pharmaceutically acceptable salt or prodrug thereof,

**[0009]** wherein $R^A$ is —$CO_2H$, —$CO_2R^B$, —CN, tetrazolyl, —C(=O)$NH_2$, —C(=O)$NHR^B$, —C(=O)$NHSO_2R^B$ or —C(=O)$NHCH_2CH_2SO_3H$ or has the structure;



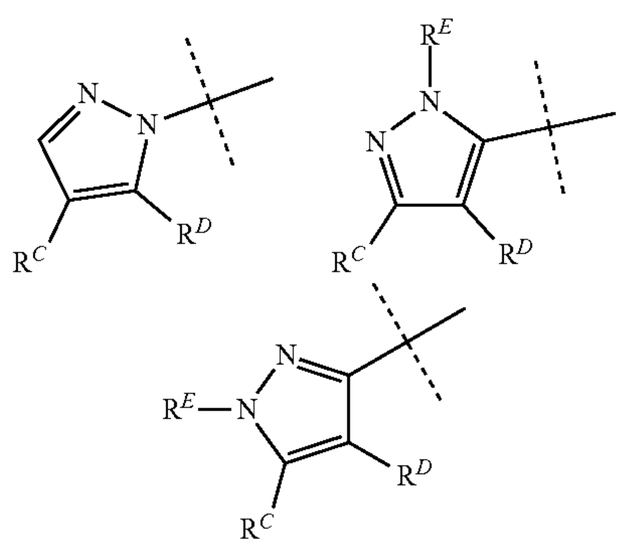
**[0010]** $R^B$ is optionally substituted $C_1$-$C_4$ alkyl or has the structure of one of



**[0011]** $L^1$ is substituted or unsubstituted $C_1$-$C_6$ alkylene, substituted or unsubstituted $C_1$-$C_6$ fluoroalkylene, substituted or unsubstituted $C_3$-$C_8$ cycloalkylene, substituted or unsubstituted $C_1$-$C_6$ heteroalkylene;

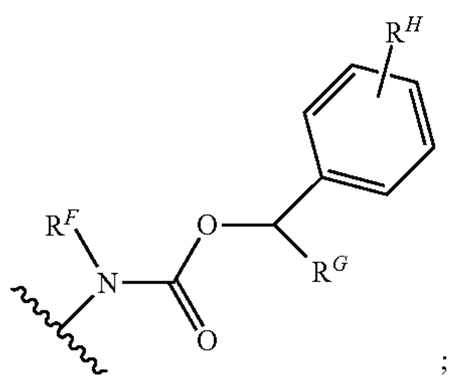
**[0012]** wherein A1 is —N═ or —CH;

**[0013]** wherein Ring A has the structure of one of



**[0014]** wherein $R^C$ is —CN, —F, —Cl, —Br, —I, —$OC_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, or $C_1$-$C_4$ fluoroalkyl;

**[0015]** and $R^D$ is —$N(R^F)$—$C(=O)XCH(R^G)$—CY, wherein X is O and CY is phenyl substituted with one $R^H$:



**[0016]** $R^E$, $R^F$ and $R^G$ independently are —H or $C_1$-$C_4$ alkyl or $C_3$-$C_6$ cycloalkyl or $R^E$ and $R^F$ independently are —H or $C_1$-$C_4$ alkyl or $C_1$-$C_6$ cycloalkyl and one $R^G$ is —$C_1$-$C_4$ alkyl and is taken together with the $R^H$ pheny moiety of the Ring A $R^D$ substituent and the carbon atom to which $R^G$ and said phenyl moiety is attached to define a substituted or unsubstituted carbocycle or a substituted or unsubstituted heterocycle;

**[0017]** $R^H$ is independently —H, halogen, —CN, —$NO_2$, —OH, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ fluoroalkyl, $C_1$-$C_4$ fluoroalkoxy, or $C_1$-$C_4$ alkoxy,

**[0018]** Other compounds of the invention have the structures indicated by the numbered embodiment and claims herein.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

**[0019]** As used herein and unless otherwise stated or implied by context, terms that are used herein have the meanings defined below. Unless otherwise contraindicated or implied, e.g., by including mutually exclusive elements or options, in these definitions and throughout this specification, the terms "a" and "an" mean one or more and the term "or" means and/or where permitted by context. Thus, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

**[0020]** At various locations in the present disclosure, e.g., in any disclosed Embodiments or in the claims, reference is made to compounds, compositions, or methods that "comprise" one or more specified components, elements or steps. Invention Embodiments also specifically include those compounds, compositions, compositions or methods that are or that consist of or that consist essentially of those specified components, elements or steps. The terms "comprising", "consist of" and "consist essentially of" have their normally accepted meanings under U.S. patent law unless otherwise specifically stated. The term "comprised of" is used interchangeably with the term "comprising" and are stated as equivalent terms. For example, disclosed compositions, devices, articles of manufacture or methods that "comprise" a component or step are open and they include or read on those compositions or methods plus an additional component(s) or step(s). Similarly, disclosed compositions, devices, articles of manufacture or methods that "consist of" a component or step are closed and they would not include or read on those compositions or methods having appreciable amounts of an additional component(s) or an additional step(s). Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed.

**[0021]** "Bond" or "single bond" as used herein means a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. As explicitly stated or implied by context, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

**[0022]** "Membered ring" as used herein means any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, by way of example and not limitation, those membered rings include cyclohexyl, pyridinyl, pyranyl and thiopyranyl, which are 6-membered rings and cyclopentyl, pyrrolyl, furanyl, and thienyl, which are 5-membered rings.

**[0023]** "Moiety" as used herein means a specific segment, fragment or functional group of a molecule or compound.

Chemical moieties are sometimes indicated as chemical entities that are embedded in or appended (i.e., a substituent or variable group) to a molecule or compound.

**[0024]** "Alkyl" as used herein is a collection of carbon atoms that are covalently linked together in normal, secondary, tertiary or cyclic arrangements, i.e., in a linear, branched, cyclic arrangement or some combination thereof. An alkyl substituent to a structure is that chain of carbon atoms that is covalently attached to the structure through a $sp^3$ carbon of the substituent. The alkyl substituents, as used herein, contains one or more saturated moieties or groups and may additionally contain unsaturated alkyl moieties or groups, i.e., the substituent may comprise one, two, three or more independently selected double bonds or triple bonds of a combination thereof, typically one double or one triple bond if such unsaturated alkyl moieties or groups are present.

**[0025]** Unsaturated alkyl moieties or groups include moieties or groups as described below for alkenyl, alkynyl, cycloalkyl, and aryl moieties. Saturated alkyl moieties contain saturated carbon atoms ($sp^3$) and no aromatic, $sp^2$ or sp carbon atoms. The number of carbon atoms in an alkyl moiety or group can vary and typically is 1 to about 50, e.g., about 1-30 or about 1-20, unless otherwise specified, e.g., $C_{1\text{-}8}$ alkyl or C1-C8 alkyl means an alkyl moiety containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms and $C_{1\text{-}6}$ alkyl or C1-C6 means an alkyl moiety containing 1, 2, 3, 4, 5 or 6 carbon atoms.

**[0026]** When an alkyl substituent, moiety or group is specified, species may include methyl, ethyl, 1-propyl (n-propyl), 2-propyl (iso-propyl, —$CH(CH_3)_2$), 1-butyl (n-butyl), 2-methyl-1-propyl (iso-butyl, —$CH_2CH(CH_3)_2$), 2-butyl (sec-butyl, —$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-butyl, —$C(CH_3)_3$), amyl, isoamyl, sec-amyl and other linear, cyclic and branch chain alkyl moieties. Unless otherwise specified, alkyl groups can contain species and groups described below for cycloalkyl, alkenyl, alkynyl groups, aryl groups, arylalkyl groups, alkylaryl groups and the like.

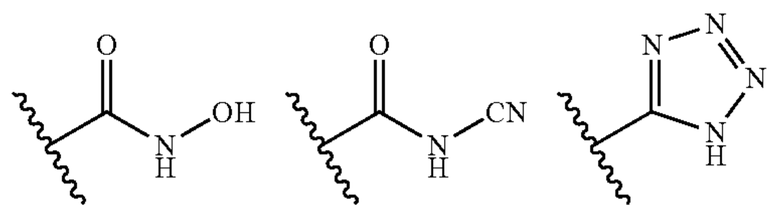
**[0027]** Cycloalkyl as used here is a monocyclic, bicyclic or tricyclic ring system composed of only carbon atoms. The term "cycloalkyl" encompasses a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. The number of carbon atoms in an cycloalkyl substituent, moiety or group can vary and typically is 3 to about 50, e.g., about 1-30 or about 1-20, unless otherwise specified, e.g., $C_{3\text{-}8}$ alkyl or C3-C8 alkyl means an cycloalkyl substituent, moiety or group containing 3, 4, 5, 6, 7 or 8 carbon atoms and $C_{3\text{-}6}$ alkyl or C3-C6 means an cycloalkyl substituent, moiety or group containing 3, 4, 5 or 6 carbon atoms. Cycloalkyl substituents, moieties or groups will typically have 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms and may contain exo or endo-cyclic double bonds or endo-cyclic triple bonds or a combination of both wherein the endo-cyclic double or triple bonds, or the combination of both, do not form a cyclic conjugated system of 4n+2 electrons; wherein the bicyclic ring system may share one (i.e., spiro ring system) or two carbon atoms and the tricyclic ring system may share a total of 2, 3 or 4 carbon atoms, typically 2 or 3.

**[0028]** Unless otherwise specified, cycloalkyl substituents, moieties or groups can contain moieties and groups described for alkenyl, alkynyl, aryl, arylalkyl, alkylaryl and the like and can contain one or more other cycloalkyl moieties. Thus, cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring, and the points of attachment to the aromatic ring are at a carbon or carbons of the cycloalkyl substituent, moiety or group that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Cycloalkyl substituents, moieties or groups include cyclopropyl, cyclopentyl, cyclohexyl, adamantly or other cyclic all carbon containing moieties. Cycloalkyls further include cyclobutyl, cyclopentenyl, cyclohexenyl, cycloheptyl and cyclooctyl. Cycloalkyl groups may be substituted or unsubstituted. Depending on the substituent structure, a cycloalkyl substituent can be a monoradical or a diradical (i.e., an cycloalkylene, such as, but not limited to, cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentan-1,1-diyl, cyclohexan-1,1-diyl, cyclohexan-1,4-diyl, cycloheptan-1,1-diyl, and the like). When cycloalkyl is used as a Markush group (i.e., a substituent) the cycloalkyl is attached to a Markush formula with which it is associated through a carbon involved in a cyclic carbon ring system carbon of the cycloalkyl group that is not an aromatic carbon.

**[0029]** "Alkylamine" as used herein means an —$N(alkyl)_xH_y$ group, moiety or substituent where x and y are independently selected from the group x=1, y=1 and x=2, y=O. Alkylamine includes those —$N(alkyl)_xH_y$ groups wherein x=2 and y=0 and the alkyl groups taken together with the nitrogen atom to which they are attached form a cyclic ring system.

**[0030]** "Heteroalkylene" as used herein means an alkylene (i.e. alkanediyl) group, moiety or substituent in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. Heteroalkylene includes $C_1$-$C_6$ heteroalkylene or $C_1$-$C_4$ heteroalkylene. Exemplary heteroalkylenes include, but are not limited to, —$OCH_2$—, —$OCH(CH_3)$—, —$OC(CH_3)_2$—, —$OCH_2CH_2$—, —$CH_2O$—, —$CH(CH_3)O$—, $C(CH_3)_2O$—, —$CH_2CH_2O$—, —$CH_2OCH_2$—, —$CH_2OCH_2CH_2$—, —$CH_2CH_2OCH_2$—, —$SCH_2$—, —$SCH(CH_3)$—, —$SC(CH_3)_2$—, —$SCH_2CH_2$—, —$CH_2S$—, —$CH(CH_3)S$—, —$C(CH_3)_2S$—, —$CH_2CH_2S$—, —$CH_2SCH_2$—, —$CH_2SCH_2CH_2$—, —$CH_2CH_2SCH_2$—, —$S(=O)_2CH_2$—, —$S(=O)_2CH(CH_3)$—, —$S(=O)_2C(CH_3)_2$—, —$S(=O)_2CH_2CH_2$—, —$CH_2S(=O)_2$—, —$CH(CH_3)S(=O)_2$—, —$C(CH_3)_2S(=O)_2$—, —$CH_2CH_2S(=O)_2$—, —$CH_2S(=O)_2CH_2$—, —$CH_2S(=O)_2CH_2CH_2$—, $CH_2CH_2S(=O)_2CH_2$—, —$NHCH_2$—, —$NHCH(CH_3)$—, —$NHC(CH_3)_2$—, —$NHCH_2CH_2$—, —$CH_2NH$—, —$CH(CH_3)NH$—, —$C(CH_3)_2NH$—, —$CH_2CH_2NH$—, —$CH_2NHCH_2$—, —$CH_2NHCH_2CH_2$—, —$CH_2CH_2NHCH_2$—, and the like.

**[0031]** "Carboxylic acid bioisostere" as used herein means a functional group, moiety or substituent that exhibits similar physical, biological and/or chemical properties as a carboxylic acid moiety. By way of example and not limitation, carboxylic acid bioisosteres include,



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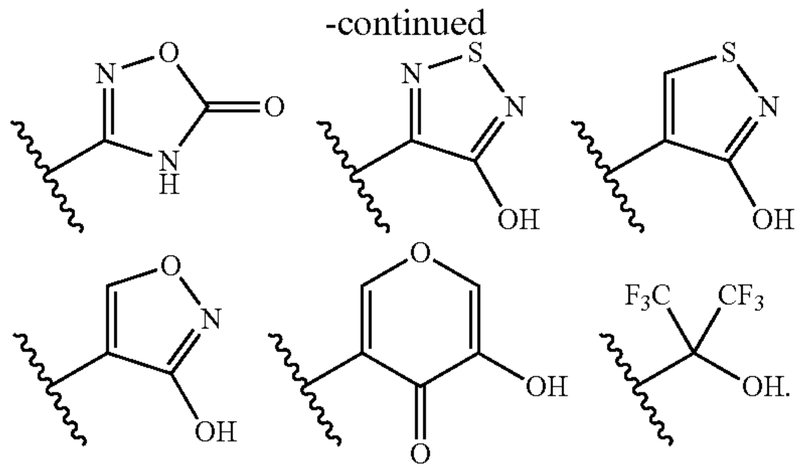


**[0032]** "Alkenyl" as used herein means a substituent, moiety or group that comprises one or more double bond moieties (e.g., —CH═CH—) or 1, 2, 3, 4, 5 or 6 or more, typically 1, 2 or 3 such moieties and can include an aryl moiety or group such as benzene, and additionally comprises linked normal, secondary, tertiary or cyclic carbon atoms, i.e., linear, branched, cyclic or any combination thereof unless the alkenyl moiety is a vinyl moiety (e.g., —CH═$CH_2$). An alkenyl moiety, group or substituent with multiple double bonds may have the double bonds arranged contiguously (i.e. a 1,3 butadienyl moiety) or non-contiguously with one or more intervening saturated carbon atoms or a combination thereof, provided that a cyclic, contiguous arrangement of double bonds do not form a cyclically conjugated system of 4n+2 electrons (i.e., aromatic). The number of carbon atoms in an alkenyl group or moiety can vary and typically is 2 to about 50, e.g., about 2-30 or about 2-20, unless otherwise specified, e.g., $C_{2-8}$ alkenyl or C2-8 alkenyl means an alkenyl moiety containing 2, 3, 4, 5, 6, 7 or 8 carbon atoms and $C_{2-6}$ alkenyl or C2-6 alkenyl means an alkenyl moiety containing 2, 3, 4, 5 or 6 carbon atoms. Alkenyl moieties or groups will typically have 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms.

**[0033]** When an alkenyl moiety, group or substituent is specified, species include, by way of example and not limitation, any of the alkyl or cycloalkyl, groups moieties or substituents described herein that has one or more double bonds, methylene (═$CH_2$), methylmethylene (═CH—$CH_3$), ethylmethylene (═CH—$CH_2$—$CH_3$), ═CH—$CH_2$—$CH_2$—$CH_3$, vinyl (—CH═$CH_2$), allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl and other linear, cyclic and branched chained all carbon containing moieties containing at least one double bond. When alkenyl is used as a Markush group (i.e., a substituent) the alkenyl is attached to a Markush formula with which it is associated through an unsaturated carbon of a double bond of the alkenyl moiety or group unless specified otherwise.

**[0034]** "Alkynyl" as used herein means a substituent, moiety or group that comprises one or more triple bond moieties (i.e., —C≡C—), e.g., 1, 2, 3, 4, 5, 6 or more, typically 1 or 2 triple bonds, optionally comprising 1, 2, 3, 4, 5, 6 or more double bonds, with the remaining bonds (if present) being single bonds and comprising linked normal, secondary, tertiary or cyclic carbon atoms, i.e., linear, branched, cyclic or any combination thereof, unless the alkynyl moiety is ethynyl. The number of carbon atoms in an alkenyl moiety or group can vary and typically is 2 to about 50, e.g., about 2-30 or about 2-20, unless otherwise specified, e.g., $C_{2-8}$ alkynyl or C2-8 alkynyl means an alkynyl moiety containing 2, 3, 4, 5, 6, 7 or 8 carbon atoms. Alkynyl groups will typically have 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms.

**[0035]** When an alkynyl moiety or group is specified, species include, by way of example and not limitation, any of the alkyl moieties, groups or substituents described herein that has one or more double bonds, ethynyl, propynyl, butynyl, iso-butynyl, 3-methyl-2-butynyl, 1-pentynyl, cyclopentynyl, 1-methyl-cyclopentynyl, 1-hexynyl, 3-hexynyl, cyclohexynyl and other linear, cyclic and branched chained all carbon containing moieties containing at least one triple bond. When an alkynyl is used as a Markush group (i.e., a substituent) the alkynyl is attached to a Markush formula with which it is associated through one of the unsaturated carbons of the alkynyl functional group.

**[0036]** "Aromatic" as used herein refers to a planar ring having a delocalized pi-electron system containing 4n+2 pi electrons, where n is a positive integer. Aromatic rings can be formed from five, six, seven, eight, nine, ten, or more than ten atoms. Aromatics are optionally substituted. The term "aromatic" includes both carboxcylic aryl ("aryl", e.g., phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups.

**[0037]** "Aryl" as used here means an aromatic ring system or a fused ring system with no ring heteroatoms comprising 1, 2, 3 or 4 to 6 rings, typically 1 to 3 rings, wherein the rings are composed of only carbon atoms; and refers to a cyclically conjugated system of 4n+2 electrons (Huckel rule), typically 6, 10 or 14 electrons some of which may additionally participate in exocyclic conjugation (cross-conjugated (e.g., quinone). Aryl substituents, moieties or groups are typically formed by five, six, seven, eight, nine, or more than nine, carbon atoms. Aryl substituents, moieties or groups are optionally substituted. Exemplary aryls include $C_6$-$C_{10}$ aryls such as phenyl and naphthalenyl and phenanthryl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group). Exemplary arylenes include, but are not limited to, phenyl-1,2-ene, phenyl-1,3-ene, and phenyl-1,4-ene. When aryl is used as a Markush group (i.e., a substituent) the aryl is attached to a Markush formula with which it is associated through an aromatic carbon of the aryl group.

**[0038]** "Arylalkyl" as used herein means a substituent, moiety or group where an aryl moiety is bonded to an alkyl moiety, i.e., -alkyl-aryl, where alkyl and aryl groups are as described above, e.g., —$CH_2$—$C_6H_5$ or —$CH_2CH(CH_3)$—$C_6H_5$. When arylalkyl is used as a Markush group (i.e., a substituent) the alkyl moiety of the arylalkyl is attached to a Markush formula with which it is associated through a $sp^3$ carbon of the alkyl moiety.

**[0039]** "Alkylaryl" as used herein means a substituent, moiety or group where an alkyl moiety is bonded to an aryl moiety, i.e., -aryl-alkyl, where aryl and alkyl groups are as described above, e.g., —$C_6H_4$—$CH_3$ or —$C_6H_4$—$CH_2CH(CH_3)$. When alkylaryl is used as a Markush group (i.e., a substituent) the aryl moiety of the alkylaryl is attached to a Markush formula with which it is associated through a $sp^2$ carbon of the aryl moiety.

**[0040]** "Substituted alkyl", "substituted cycloalkyl", "substituted alkenyl", "substituted alkynyl", substituted alkylaryl", "substituted arylalkyl", "substituted heterocycle",

"substituted aryl" and the like as used herein mean an alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl heterocycle, aryl or other group or moiety as defined or disclosed herein that has a substituent(s) that replaces a hydrogen atom(s) or a substituent(s) that interrupts a carbon atom chain. Alkenyl and alkynyl groups that comprise a substituent(s) are optionally substituted at a carbon that is one or more methylene moieties removed from the double bond.

**[0041]** "Optionally substituted alkyl", "optionally substituted alkenyl", "optionally substituted alkynyl", "optionally substituted alkylaryl", "optionally substituted arylalkyl", "optionally substituted heterocycle", "optionally substituted aryl", "optionally substituted heteroaryl", "optionally substituted alkylheteroaryl", "optionally substituted heteroarylalkyl" and the like as used herein mean an alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl heterocycle, aryl, heteroaryl, alkylheteroaryl, heteroarylalkyl, or other substituent, moiety or group as defined or disclosed herein that has a substituent (s) that optionally replaces a hydrogen atom(s) or a substituent(s) that interrupts a carbon atom chain. Such substituents are as described herein. For a phenyl moiety, the arrangement of any two substituents present on the aromatic ring can be ortho (o), meta (m), or para (p). An optionally substituted fluoroalkyl is an alkyl or cycloalkyl moiety, typically a linear alkyl, wherein one or more hydrogen atoms is replaced by fluorine and at least one other atom other than carbon and fluorine.

**[0042]** An optionally substituted or substituted substituent, moiety or group includes those having one or more additional group(s) that replace its hydrogen atom(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, nitro, haloalkyl, fluoroalkyl, fluoroalkoxy, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. By way of example and not limitation an optional substituent(s) may be halide, —CN, —$NO_2$, or LsRs, wherein each Ls is independently selected from a bond, —O—, —C(═O)—, —C(═O)O—, —S—, —S(═O)—, —$S(═O)_2$—, —NH—, —NHC(═O)—, —C(═O)NH—, $S(═O)_2NH$—, —$NHS(═O)_2$, —OC(═O)NH—, —NHC(═O)O—, or —($C_1$-$C_6$ alkylene)-; and each Rs is selected from —H, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. The protecting groups that may form the protective derivatives of the above substituents may be found in sources such as Greene and Wuts, above. Optional substituents include those selected from the group consisting of halogen, —CN, —$NH_2$, —OH, —$N(CH_3)_2$, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone, those selected from the group consisting of halogen, —CN, —$NH_2$, —OH, $NH(CH_3)$, —$N(CH_3)_2$, —$CO_2H$, —$CO_2$alkyl, —C(═O)$NH_2$, —C(═O)NHalkyl, —C(═O)$N(alkyl)_2$, —$S(═O)_2NH_2$, —$S(═O)_2NH(alkyl)$, —$S(═O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, —S-alkyl and —$S(═O)_2$alkyl or those selected from the group consisting of halogen, —CN, —$NH_2$, —OH, —$NH(CH_3)$, —$N(CH_3)_2$, —$CH_3$, —$CH_2CH_3$, —$CF_3$, —$OCH_3$, and —$OCF_3$. Typically, an optionally substituted, substituent, moiety or group is substituted with one or two of the preceding groups, or more typically with one of the preceding groups. An optional substituent on an aliphatic carbon atom (acyclic or cyclic, saturated or unsaturated carbon atoms, excluding aromatic carbon atoms) further includes oxo (═O).

**[0043]** "Heterocycle" or "heterocyclic" as used herein means a cycloalkyl or aromatic ring system wherein one or more, typically 1, 2 or 3, but not all of the carbon atoms comprising the ring system are replaced by a heteroatom which is an atom other than carbon, including, N, O, S, Se, B, Si, P, typically N, O or S wherein two or more heteroatoms may be adjacent to each other or separated by one or more carbon atoms, typically 1-17 carbon atoms, 1-7 atoms or 1-3 atoms. Heterocycles includes heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the any ring does not contain two adjacent O or S atoms.

**[0044]** Non-aromatic heterocyclic, substituents, moieties or groups (also known as heterocycloalkyls) have at least 3 atoms in their ring system, and aromatic heterocyclic groups have at least 5 atoms in their ring system and include benzo-fused ring systems. Heterocyclics with 3, 4, 5, 6 and 10 atoms include aziridinyl azetidinyl, thiazolyl, pyridyl and quinolinyl, respectively. Nonaromatic heterocyclic substituents, moieties or groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0)hexanyl, 3azabicyclo[4.1.0)heptanyl, 3H-indolyl and quinolizinyl. Aromatic heterocyclic includes, by way of example and not limitation, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzo-thiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Non-aromatic heterocycles may be substituted with one or two oxo (═O) moieties, and includes pyrrolidin-2-one.

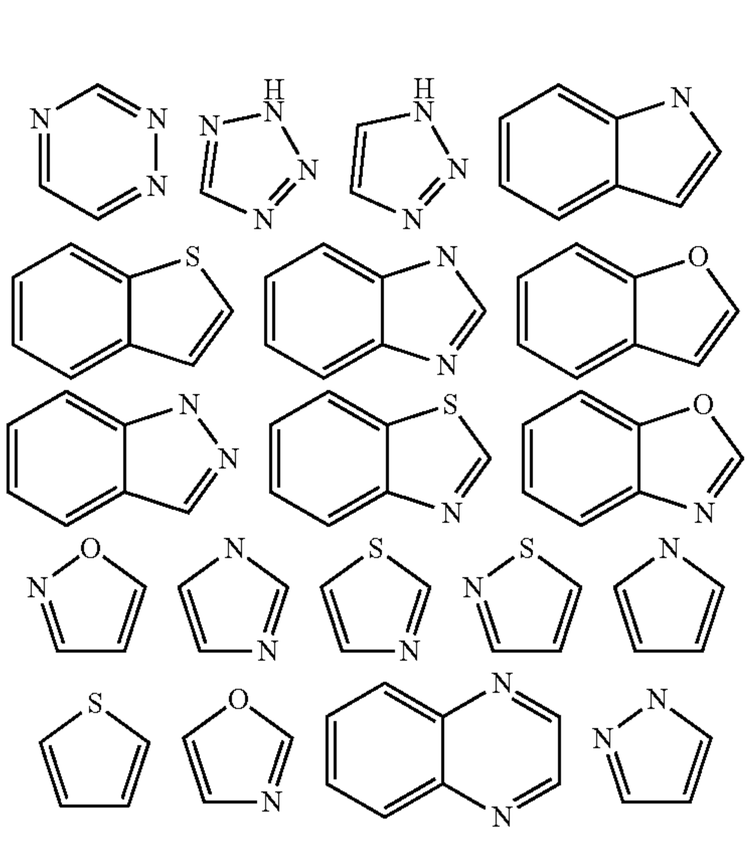
**[0045]** When heterocycle is used as a Markush group (i.e., a substituent) the heterocycle is attached to a Markush formula with which it is associated through a carbon or a heteroatom of the heterocycle, where such an attachment does not result in an unstable or disallowed formal oxidation state of that carbon or heteroatom. A heterocycle that is C-linked is bonded to a molecule through a carbon atom include moieties such as —$(CH_2)_n$-heterocycle where n is 1, 2 or 3 or —C<heterocycle where C<represents a carbon atom in a heterocycle ring. A heterocycle that is N-linked is a nitrogen containing heterocycle that is bonded a heterocycle ring nitrogen sometimes described as —N<heterocycle where N<represents a nitrogen atom in a heterocycle ring. Thus, nitrogen-containing heterocycles

may be C-linked or N-linked and include pyrrole substituents, which may be pyrrol-1-yl (N-linked) or pyrrol-3-yl (C-linked), imidazole substituents, which may be imidazol-1-yl or imidazol-3-yl (both N-linked) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-linked).

**[0046]** "Heteroaryl" as used herein means an aryl ring system wherein one or more, typically 1, 2 or 3, but not all of the carbon atoms comprising the aryl ring system are replaced by a heteroatom which is an atom other than carbon, including, N, O, S, Se, B, Si, P, typically, oxygen (—O—), nitrogen (—NX—) or sulfur (—S—) where X is —H, a protecting group or $C_{1-6}$ optionally substituted alkyl, wherein the heteroatom participates in the conjugated system either through pi-bonding with an adjacent atom in the ring system or through a lone pair of electrons on the heteroatom and may be optionally substituted on one or more carbons or heteroatoms, or a combination of both, in a manner which retains the cyclically conjugated system.

**[0047]** Heterocycles and heteroaryls, include, by way of example and not limitation, heterocycles and heteroaryls described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* 1960, 82:5545-5473 particularly 5566-5573). Examples of heteroaryls include by way of example and not limitation pyridyl, thiazolyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, purinyl, imidazolyl, benzofuranyl, indolyl, isoindoyl, quinolinyl, isoquinolinyl, benzimidazolyl, pyridazinyl, pyrazinyl, benzothiopyran, benzotriazine, isoxazolyl, pyrazolopyrimidinyl, quinoxalinyl, thiadiazolyl, triazolyl and the like. Heterocycles that are not heteroaryls include, by way of example and not limitation, tetrahydrothiophenyl, tetrahydrofuranyl, indolenyl, piperidinyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, 2H-pyrrolyl, 3H-indolyl, 4H-quinolizinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, piperazinyl, quinuclidinyl, morpholinyl, oxazolidinyl and the like.

**[0048]** Other heteroaryls include, by way of example and not limitation, the following moieties:



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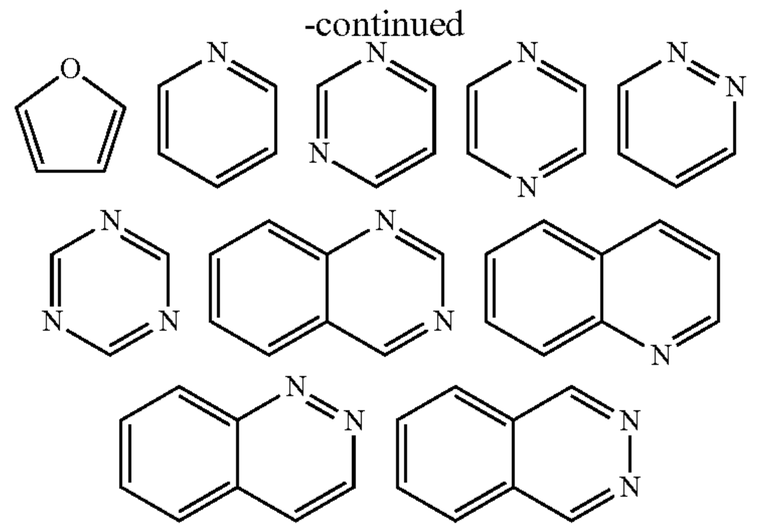
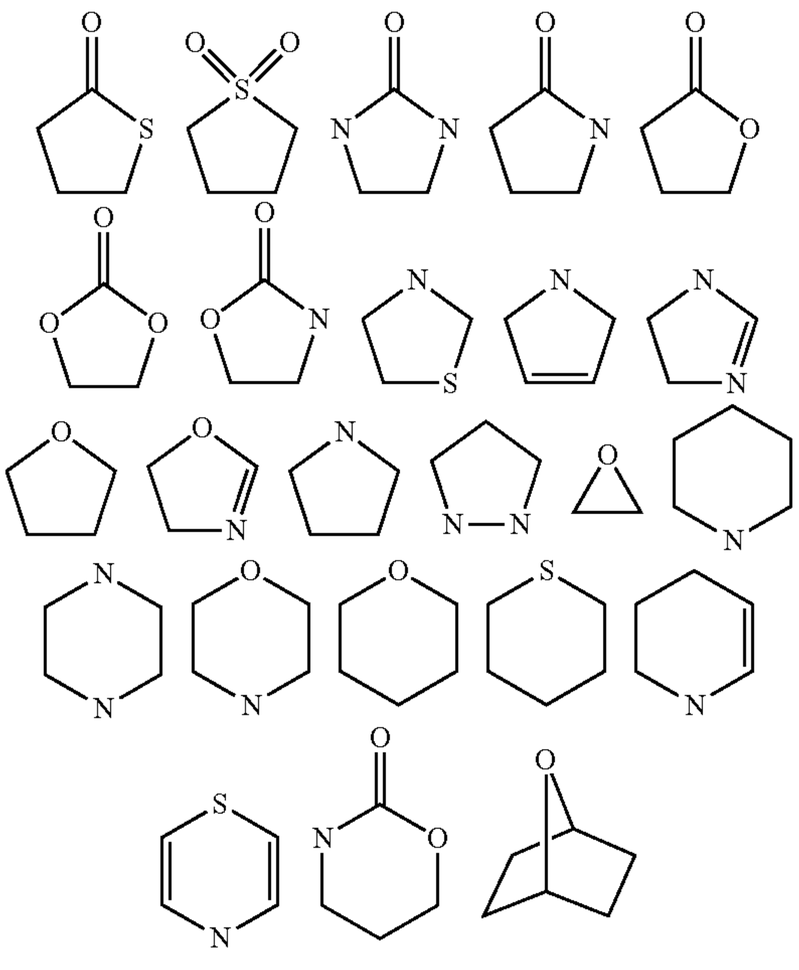


**[0049]** Monocyclic heteroaryls include, by way of example and not limitation, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Heteroaryls include those substituents, moieties or groups containing 0-3 N atoms, 1-3 N atoms or 0-3 N atoms, 0-1 O atoms and 0-1 S atoms. A heteroaryl may be monocyclic or bicyclic. The ring system of a heteroaryls ring typically contains 1-9 carbons (i.e., $C_1$-$C_9$ heteroaryl). Monocyclic heteroaryls include $C_1$-$C_5$ heteroaryls. Monocyclic heteroaryls include those having 5-membered or 6-membered ring systems. Bicyclic heteroaryls include $C_5$-$C_9$ heteroaryls. Depending on the structure, a heteroaryl group can be a monoradical or a diradical (i.e., a heteroarylene group).

**[0050]** "Heterocycloalkyl" or "heteroalicyclic" as used herein means a cycloalkyl group, moiety or substituent wherein at least on carbon of the cycloalkyl chain is replaces with a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur. The heterocycloalkyl may be fused with an aryl or heteroaryl. Heterocycloalkyls, also referred to as non-aromatic heterocycles, include by way of example and not limitation:



**[0051]** Heterocycloalkyl includes, by way of example and not limitation, oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and indolinyl. Heteroalicyclics further includes all ring forms of carbohydrates, including but not limited to monosaccharides, disaccharides and oligosaccharides. Typically, a heterocycloalkyl is a $C_2$-$C_{10}$ heterocycloalkyl and includes $C_4$-$C_{10}$ heterocycloalkyl. A heterocycloalkyl may contain 0-2 N atoms, 0-2 O atoms or 0-1 S atoms.

**[0052]** "Heteroarylalkyl" as used herein means a substituent, moiety or group where a heteroaryl moiety is bonded to an alkyl moiety, i.e., -alkyl-heteroaryl, where alkyl and heteroaryl groups are as described above. When heteroarylalkyl is used as a Markush group (i.e., a substituent) the alkyl moiety of the heteroarylalkyl is attached to a Markush formula with which it is associated through a $sp^3$ carbon of the alkyl moiety.

**[0053]** "Alkylheteroaryl" as used herein means a substituent, moiety or group where a heteroaryl moiety is bonded to an alkyl moiety, i.e., -heteroaryl-alkyl, where heteroaryl and alkyl groups are as described above. When heteroarylalkyl is used as a Markush group (i.e., a substituent) the heteroaryl moiety of the heteroarylalkyl is attached to a Markush formula with which it is associated through a $sp^2$ carbon or heteroatom of the alkyl moiety.

**[0054]** "Halogen" or "halo" as used herein means fluorine, chlorine, bromine or iodine.

**[0055]** "Haloalkyl" as used herein means an alkyl substituent moiety or group in which one or more of its hydrogen atoms are replaced by one or more independently selected halide atoms. Haloalkyl includes $C_1$-$C_4$ haloalkyl. Example but non-limiting $C_1$-$C_4$ haloalkyls are —$CH_2Cl$, $CH_2Br$, —$CH_2I$, —CHBrCl, —CHCl—$CH_2Cl$ and —CHCl—$CH_2I$.

**[0056]** "Haloalkylene" as used herein means an alkylene substituent, moiety or group in which one or more hydrogen atoms are replaced by one or more halide atoms. Haloalkylene includes $C_1$-$C_6$ haloalkylenes or $C_1$-$C_4$ haloalkylenes.

**[0057]** "Fluoroalkyl" as used herein means an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. Fluoroalkyl includes $C_1$-$C_6$ and $C_1$-$C_4$ fluoroalkyls. Example but non-limiting fluoroalkyls include —$CH_3F$, —$CH_2F_2$ and —$CF_3$ and perfluroalkyls.

**[0058]** "Fluoroalkylene" as used herein means an alkylene in which one or more hydrogen atoms are replaced by a fluorine atom. Fluoroalkylene includes $C_1$-$C_6$ fluoroalkylenes or $C_1$-$C_4$ fluoroalkylenes.

**[0059]** The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. In one aspect, a heteroalkyl is a C1-C6 heteroalkyl.

**[0060]** "Protecting group" as used here means a moiety that prevents or reduces the ability of the atom or functional group to which it is linked from participating in unwanted reactions. Non-limiting examples are for —$OR^{PR}$, wherein $R^{PR}$ is a protecting group for the oxygen atom found in a hydroxyl, while for —C(O)—$OR^{PR}$, $R^{PR}$ may be a carboxylic acid protecting group; for —$SR^{PR}$, $R^{PR}$ may be a protecting group for sulfur in thiols and for —$NHR^{PR}$ or —$N(R^{PR})_2$—, at least one of $R^{PR}$ is a nitrogen atom protecting group for primary or secondary amines. Hydroxyl, amine, ketones and other reactive groups may require protection against reactions taking place elsewhere in the molecule. The protecting groups for oxygen, sulfur or nitrogen atoms are usually used to prevent unwanted reactions with electrophilic compounds, such as acylating agents. Typical protecting groups for atoms or functional groups are given in Greene (1999), "Protective groups in organic synthesis, $3^{rd}$ ed.", Wiley Interscience.

**[0061]** "Ester" as used herein means a substituent, moiety or group that contains a —C(O)—O— structure (i.e., ester functional group) wherein the carbon atom of the structure is not directly connected to another heteroatom and is directly connected to —H or another carbon atom. Typically, esters comprise or consist of an organic moiety containing 1-50 carbon atoms, 1-20 carbon atoms or 1-8 carbon atoms and 0 to 10 independently selected heteroatoms (e.g., O, S, N, P, Si), typically 0-2 where the organic moiety is bonded through the —C(O)—O— structure and include ester moieties such as organic moiety-C(O)—O—. The organic moiety usually comprises one or more of any of the organic groups described herein, e.g., $C_{1\text{-}20}$ alkyl moieties, $C_{2\text{-}20}$ alkenyl moieties, $C_{2\text{-}20}$ alkynyl moieties, aryl moieties, $C_{3\text{-}8}$ heterocycles or substituted derivatives of any of these, e.g., comprising 1, 2, 3, 4 or more substituents, where each substituent is independently chosen. Exemplary, non-limiting substitutions for hydrogen or carbon atoms in these organic groups are as described above for substituted alkyl and other substituted moieties and are independently chosen. The substitutions listed above are typically substituents that one can use to replace one or more carbon atoms, e.g., —O— or —C(O)—, or one or more hydrogen atom, e.g., halogen, —$NH_2$ or —OH. Exemplary esters include by way of example and not limitation, one or more independently selected acetate, propionate, isopropionate, isobutyrate, butyrate, valerate, isovalerate, caproate, isocaproate, hexanoate, heptanoate, octanoate, phenylacetate esters or benzoate esters. When ester is used as a Markush group (i.e., a substituent) the single bonded oxygen of the ester functional group is attached to a Markush formula with which it is associated.

**[0062]** "Acetal", "thioacetal", "ketal", "thioketal" and the like as used herein means a moiety, group or substituent comprising or consisting of a carbon to which is bonded two of the same or different heteroatoms wherein the heteroatoms are independently selected S and O. For acetal the carbon has two bonded oxygen atoms, a hydrogen atom and an organic moiety. For ketal, the carbon has two bonded oxygen atoms and two independently selected organic moieties where the organic moiety is as described herein alkyl or optionally substituted alkyl group. For thioacetals and thioketals one or both of the oxygen atoms in acetal or ketal, respectively, is replaced by sulfur. The oxygen or sulfur atoms in ketals and thioketals are sometimes linked by an optionally substituted alkyl moiety. Typically, the alkyl moiety is an optionally substituted $C_{1\text{-}8}$ alkyl or branched alkyl structure such as —$C(CH_3)_2$—, —$CH(CH_3)$—, —$CH_2$—, —$CH_2$—$CH_2$—, —$C[(C_2\text{-}C_4\ \text{alkyl})_2]_{1,\ 2,\ 3}$- or —$[CH(C_2\text{-}C_4\ \text{alkyl})]_{1,\ 2,\ 3}$-. Some of these moieties can serve as protecting groups for an aldehyde or ketone include, by way of example and not limitation, acetals for aldehydes and ketals for ketones and contain —O—$CH_2$—$CH_2$—$CH_2$—O— or —O—$CH_2$—$CH_2$—O— moieties that form a

spiro ring with the carbonyl carbon, and can be removed by chemical synthesis methods or by metabolism in cells or biological fluids.

**[0063]** "Ether" as used herein means an organic moiety, group or substituent that comprises or consists of 1, 2, 3, 4 or more —O— moieties, usually 1 or 2, wherein no two —O— moieties are immediately adjacent (i.e., directly attached) to each other. Typically, ethers comprise an organic moiety containing 1-50 carbon atoms, 1-20 carbon atoms or 1-8 carbon atoms and 0 to 10 independently selected heteroatoms (e.g., O, S, N, P, Si), typically 0-2. An ether moiety, group or substituent includes organic moiety-O— wherein the organic moiety is as described herein for alkyl or optionally substituted alkyl group. When ether is used as a Markush group (i.e., a substituent) the oxygen of the ether functional group is attached to a Markush formula with which it is associated. When ether is a used as substituent in a Markush group it is sometimes designated as an "alkoxy" group. Alkoxy includes C1-C4 ether substituents such as, by way of example and not limitation, methoxy, ethoxy, propoxy, iso-propoxy and butoxy. Ether further includes those substituents, moieties or groups that contain one (excluding ketal) or more —$OCH_2CH_2O$—, moieties in sequence (i.e., polyethylene or PEG moieties).

**[0064]** "Carbonate" as used here means a substituent, moiety or group that contains a —O—C(═O)—O— structure (i.e., carbonate functional group). Typically, carbonate groups as used here comprise or consist of an organic moiety containing 1-50 carbon atoms, 1-20 carbon atoms or 1-8 carbon atoms and 0 to 10 independently selected heteroatoms (e.g., O, S, N, P, Si), typically 0-2, bonded through the —O—C(═O)—O— structure, e.g., organic moiety-O—C(═O)—O—. When carbonate is used as a Markush group (i.e., a substituent) one of the singly bonded oxygen atoms of the carbonate functional group is attached to a Markush formula with which it is associated.

**[0065]** "Carbamate" or "urethane" as used here means a substituent, moiety or group that contains a —O—C(═O)$N(R^{PR})$—, —O—C(═O)$N(R^{PR})_2$, —O—C(═O)NH(optionally substituted alkyl) or —O—C(═O)N (optionally substituted alkyl)$_2$- structure (i.e., carbamate functional group) where $R^{PR}$ and optionally substituted alkyl are independently selected and $R^{PR}$ are independently —H, a protecting group or an organic moiety as described for ester, alkyl or optionally substituted alkyl. Typically, carbamate groups as used here comprise or consist of an organic moiety containing about 1-50 carbon atoms, 1-20 carbon atoms or 1-8 carbon atoms and 0 to 10 independently selected heteroatoms (e.g., O, S, N, P, Si), typically 0-2, bonded through the —O—C(═O)—$NR^{PR}$— structure, e.g., organic moiety-O—C(═O)—$NR^{PR}$— or —O—C(═O)—$NR^{PR}$-organic moiety. When carbamate is used as a Markush group (i.e., a substituent) the singly bonded oxygen (O-linked) or nitrogen (N-linked) of the carbamate functional group is attached to a Markush formula with which it is associated. The linkage of the carbamate substituent is either explicitly stated (N- or O-linked) or implicit in the context to which this substituent is referred.

**[0066]** For any substituent group or moiety described by a given range of carbon atoms, the designated range means that any individual number of carbon atoms is described. Thus, reference to, e.g., "C1-C4 optionally substituted alkyl", "C2-6 alkenyl optionally substituted alkenyl", "C3-C8 optionally substituted heterocycle" specifically means that a 1, 2, 3 or 4 carbon optionally substituted alkyl moiety as defined herein is present, or a 2, 3, 4, 5 or 6 carbon alkenyl, or a 3, 4, 5, 6, 7 or 8 carbon moiety comprising a heterocycle or optionally substituted alkenyl moiety as defined herein is present. All such designations are expressly intended to disclose all of the individual carbon atom groups and thus "C1-C4 optionally substituted alkyl" includes, e.g., 3 carbon alkyl, 4 carbon substituted alkyl and 4 carbon alkyl, including all positional isomers and the like are disclosed and can be expressly referred to or named. For esters, carbonates and carbamates defined by a given range of carbon atoms, the designated range includes the carbonyl carbon of the respective functional group. Thus, a C1 ester refers to a formate ester and a C2 ester refers to an acetate ester. The organic substituents, moieties and groups described herein, and for other any other moieties described herein, usually will exclude unstable moieties except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for the one or more of the uses described herein. Substituents, moieties or groups by operation of the definitions herein that results in those having a pentavalent carbon are specifically excluded.

**[0067]** "LPA-dependent", "LPA-mediated" or like terms as used herein means a disease or condition whose etiology, progression or persistence is effected by in whole or in part by signaling through one or more lysophosphatidic acid receptor subtypes, including by way of example and not limitation lysophosphatidic acid receptor subtypes 1-6 (LPARs). LPA-dependent or LPA-mediated diseases and conditions include but not limited to fibrosis of organs (e.g., liver, kidney, lung, heart and the like), liver diseases (e.g., acute hepatatis, chronic hepatitis, liver fibrosis, liver cirrhosis, portal hypertension, regenerative failure, nonalcoholic steatohepatitis (NASH), liver hypofunction, hepatic blood flow disorder, and the like), cell proliferative disease (e.g., cancers, including but not limited to solid tumor, solid tumor metastasis, vascular fibroma, myeloma, multiple myeloma, Kaposi's sarcoma, leukemia, chronic lymphocytic leukemia (CLL), invasive metastasis of cancer cell, and the like), inflammatory disease (e.g., psoriasis, nephropathy, pneumonia and the like), gastrointestinal tract disease (e.g., irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), abnormal pancreatic secretion, and the like), 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, and the like), inflammatory disease of lower urinary tract (e.g., dysuria, frequent urination, and the like), pancreas disease, abnormal angiogenesis-associated disease (e.g., arterial obstruction and the like), scleroderma, brain-associated disease (e.g., cerebral infarction, cerebral hemorrhage, and the like), nervous system diseases (e.g., neuropathic pain, peripheral neuropathy, pruritus and the like), ocular disease (e.g., age-related macular degeneration (AMD), diabetic retinopathy, proliferative vitreo-retinopathy (PVR), cicatricial pemphigoid, glaucoma filtration surgery scarring, and the like).

**[0068]** "LPA1R selective agents", LPA1R selective compounds" and like terms as used herein means agents or compounds that interact with the lysophosphatidic acid subtype 1 receptor in preference to the lysophosphatidic acid

receptor 2-6. Typically, that preference is manifested by 10-fold stronger binding affinity of the agent to LPA1R in comparison to other known LPARs as measured by experimentally determined $K_D$ values.

**[0069]** "Pharmaceutically acceptable formulation" as used herein means a composition comprising an active pharmaceutical ingredient, such as a compound having the formula of I-VI in addition to one or more pharmaceutically acceptable excipients or refers to a composition prepared from an active pharmaceutical ingredient and one or more pharmaceutically acceptable excipients, wherein the composition is suitable for administration to a subject, such as a human or an animal, in need thereof. For a pharmaceutically acceptable formulation to be suitable for administration to a human the formulation must have biological activity for treating or preventing a disease or condition disclosed herein or an expectation must exist that the formulation would have a desired activity towards an "intent to treat" disease or condition. Typically, the "intent to treat" disease or condition is a lysophosphatidic acid receptor-mediated condition or disease. More typically the disease or condition to be treated or prevented is a lysophosphatidic acid lysophosphatidic acid type 1 receptor-mediated disease or condition. A pharmaceutically acceptable formulation that is suitable for administration to an animal does not necessarily require a biological activity for treating or preventing a disease or condition, and may be administered to the animal in order to evaluate a potential pharmacological or biological activity of a Formula I-XII compound. Those formulations must therefore be suitable for treating or preventing a disease or condition disclosed herein in an animal in need thereof or is suitable for evaluating a pharmacological or biological activity of a Formula I-XII compound. Compositions that are suitable only for use in vitro assays or which contain a vehicle, component or excipient in an amount not permitted in a drug product are specifically excluded from the definition of a pharmaceutically acceptable formulation.

**[0070]** The pharmaceutically acceptable formulation may be comprised of, or be prepared from, one, two or more Formula I-XII compounds, typically one or two, and one or more pharmaceutically acceptable excipients. More typically, the formulations will consist essentially of or consist of a single Formula I-XII compound and one or more pharmaceutically acceptable excipients. Other formulations may be comprised of, consist essentially of, or consist of one, two or more Formula I-XII compounds and one two or more compounds in current use for treating lysophosphatidic acid lysophosphatidic acid type 1 receptor-mediated disease or condition disclosed herein and one or more pharmaceutically acceptable excipients. Typically, those formulations will consist essentially of or consist of a single Formula I-XII compound, a single compound in current use for treating a lysophosphatidic acid lysophosphatidic acid type 1 receptor-mediated disease or condition and one or more pharmaceutically acceptable excipients.

**[0071]** "Solid formulation" as used herein refers to a pharmaceutically acceptable formulation comprising at least one Formula I-XII compound and one or more pharmaceutically acceptable excipients in solid form(s) wherein the formulation is in a unit dosage form suitable for administration of a solid. The dosage units include tablets, capsules, caplets, gelcaps, suspensions and other dosage units typically associated with parenteral or enteral (oral) administration of a solid.

**[0072]** "Liquid formulation" as used herein refers to a pharmaceutically acceptable formulation wherein at least one Formula I-XII compound has been admixed or contacted with one or more pharmaceutically acceptable excipients, wherein at least one of the excipients is in liquid form in proportions required for a liquid formulation, i.e., such that a majority of the mass amount of the Formula I-XII compound(s) is dissolved into the non-solid excipient. Dosage units containing a liquid formulation include syrups, gels, ointments and other dosage units typically associated with parenteral or enteral administration of a pharmaceutical formulation to a subject in need thereof in liquid form.

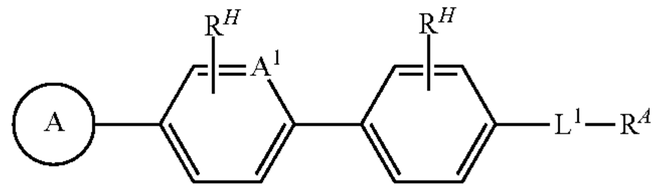
**[0073]** "Prevent, "preventing" and like terms as used herein takes on its normal and customary meaning in the medical arts and therefore does not require that each instance to which the term refers be avoided with certainty.

## NUMBERED EMBODIMENTS

**[0074]** The following embodiments exemplify the invention and are not meant to limit the invention in any manner. In certain embodiments, the compounds presented herein possess one or more stereocenters and each center independently exists in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns. The methods and formulations described herein include the use of pharmaceutically acceptable salts of compounds having the structure of Formulas (I-VI), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In specific embodiments, the compounds described herein will exist as salts, including pharmaceutically acceptable salts. The salt forms include inorganic addition salts such as $F^-$ $Cl^-$, $Br^-$, $I^-$ and sulfate salts and organic addition salts such as mesylate, besylate, tosylate, citrate, succinate, fumarate and malonate. In other embodiments, the compounds described herein exist as quaternary ammonium salts.

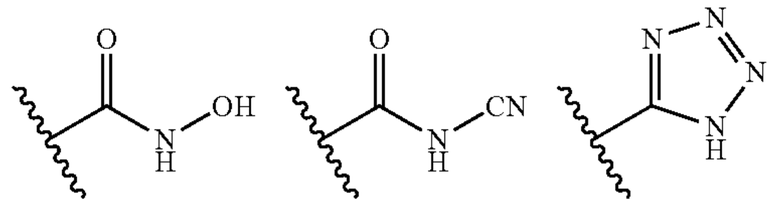
**[0075]** Embodiment 1. A compound of Formula I having the structure

Formula I



or a pharmaceutically acceptable salt or prodrug thereof,

**[0076]** wherein RA is —$CO_2H$, —$CO_2RB$, —CN, tetrazolyl, —$C(=O)NH_2$, —C(=O)NHRB, C(=O)$NHSO_2RB$ or —$C(=O)NHCH_2CH_2SO_3H$ or has the structure;



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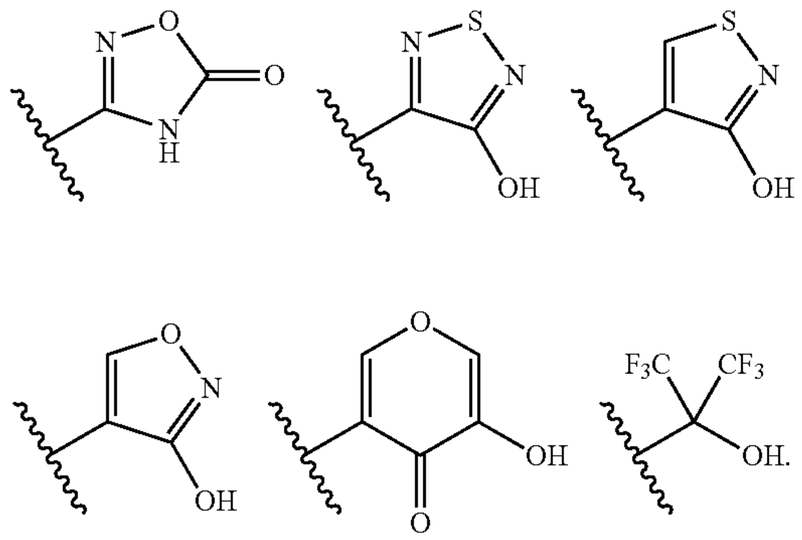
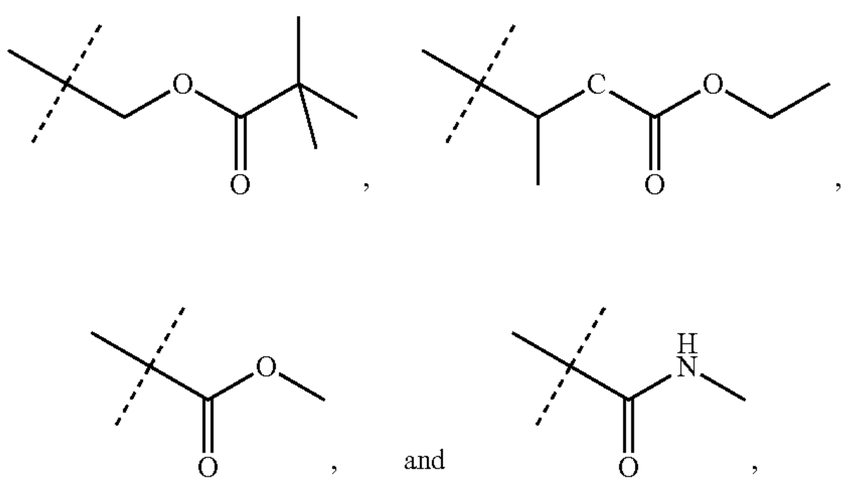


**[0077]** $R^B$ is optionally substituted $C_1$-$C_4$ alkyl or has the structure of one of



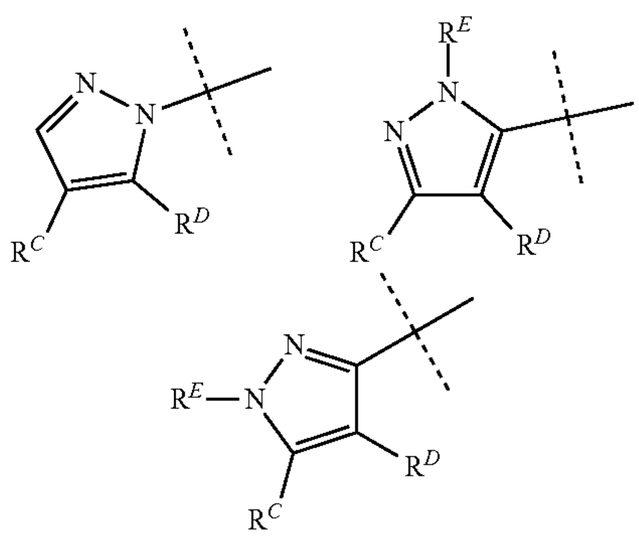
and;

**[0078]** wherein $R^B$ is substituted or unsubstituted $C_1$-$C_4$ alkyl;

**[0079]** $L^1$ is substituted or unsubstituted $C_1$-$C_6$ alkylene, substituted or unsubstituted $C_1$-$C_6$ fluoroalkylene, substituted or unsubstituted $C_3$-$C_8$ cycloalkylene, substituted or unsubstituted $C_1$-$C_6$ heteroalkylene;

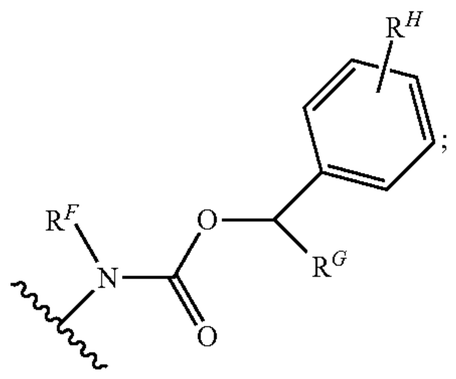
**[0080]** wherein A1 is —N═ or —CH;

**[0081]** wherein Ring A has the structure of one of



**[0082]** wherein $R^C$ is —CN, —F, —Cl, —Br, —I, —$OC_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, or $C_1$-$C_4$ fluoroalkyl;

**[0083]** and $R^D$ is —N($R^F$)—C(═O)XCH($R^G$)—CY, wherein X is O and CY is phenyl substituted with one $R^H$:



**[0084]** $R^E$, $R^F$ and $R^G$ independently are —H or $C_1$-$C_4$ alkyl or $C_3$-$C_6$ cycloalkyl or $R^E$ and $R^F$ independently are —H or $C_1$-$C_4$ alkyl or $C_1$-$C_6$ cycloalkyl and one $R^G$ is —$C_1$-$C_4$ alkyl and is taken together with the $R^H$ pheny moiety of the Ring A $R^D$ substituent and the carbon atom to which $R^G$ and said phenyl moiety is attached to define a substituted or unsubstituted carbocycle or a substituted or unsubstituted heterocycle;

**[0085]** $R^H$ is independently —H, halogen, —CN, —$NO_2$, —OH, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ fluoroalkyl, $C_1$-$C_4$ fluoroalkoxy, or $C_1$-$C_4$ alkoxy,

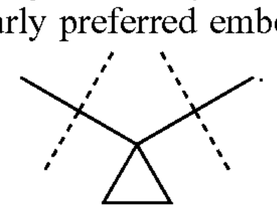
**[0086]** In some embodiments $R^C$ is —CN, —F, —Cl, —Br, —I, —$OC_1$-$C_4$ alkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, or $C_1$-$C_4$ fluoroalkyl and $R^D$ is —N($R^F$)—C(═O)OCH($R^G$)—CY,
wherein $R^F$ and each $R^G$ independently are —H or $C_1$-$C_4$ alkyl.

**[0087]** In preferred embodiments $R^A$ is —$CO_2$H, —CONHCN, tetrazolyl, or —C(═O)N$HSO_2R^B$, wherein $R^B$ is substituted or unsubstituted $C_1$-$C_4$ alkyl.

**[0088]** In particularly preferred embodiments $R^A$ is —$CO_2$H, —CONHCN, tetrazolyl, or —C(═O)N$HSO_2R^B$, wherein $R^B$ is —$CH_3$.

**[0089]** In some embodiments $L^1$ is substituted or unsubstituted $C_1$-$C_6$ alkylene, $C_1$-$C_6$ fluoroalkylene, or substituted or unsubstituted $C_1$-$C_6$ heteroalkylene.

**[0090]** In particularly preferred embodiments $L^1$ is



**[0091]** In some embodiments, Formula I compounds have $R^C$ defined as —CN, —F, —Cl, or $C_1$-$C_4$ fluoroalkyl.

**[0092]** In more preferred embodiments, Formula I compounds have $R^C$ defined as —F, or —Cl.

**[0093]** In some embodiments, Formula I compounds have $R^D$ defined as —N($R^F$)C(═O)—OCH($R^G$)—CY, wherein $R^F$ is —H or $C_1$-$C_4$ alkyl and X, CY and $R^G$ are as previously defined.

**[0094]** In more preferred embodiments, Formula I compounds have $R^D$ defined as —N($R^F$)C(═O)OCH($R^G$)—CY, wherein $R^F$ is —H and CY and $R^G$ are as previously defined.

**[0095]** In some embodiments, Formula I compounds have $R^F$ defined as H, $C_1$-$C_4$ alkyl or $C_3$-$C_6$ cycloalkyl.

**[0096]** In more preferred embodiments, Formula I compounds have $R^F$ defined as —H.

**[0097]** In some embodiments of Formula I compounds $R^G$ is independently —H or $C_1$-$C_4$ alkyl.

**[0098]** In more preferred embodiments, Formula I compounds have $R^G$ defined as —$CH_3$.

**[0099]** In some embodiments of Formula I compounds CY is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein if CY is substituted then CY is substituted with 1, 2, or 3 independently selected $R^H$.

**[0100]** In preferred Formula I compounds have $R^A$ is —$CO_2H$, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^F$, $R^G$, and CY are as previously defined.

**[0101]** In other preferred Formula I compounds $R^A$ is tetrazolyl, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^F$, $R^G$, and CY are as previously defined.

**[0102]** In other preferred Formula I compounds $R^A$ is —$C(=O)NHSO_2R^B$, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^B$, $R^F$, $R^G$, and CY are as previously defined.

**[0103]** In other preferred Formula I compounds $R^A$ is —CONHCN, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^F$, $R^G$, and CY are as previously defined.

**[0104]** Embodiment 2. The compound of Embodiment 1 wherein $R^A$ is —$CO_2H$ or CONHCN.

**[0105]** Embodiment 3. The compound of Embodiment 1 wherein $R^A$ is tetrazolyl.

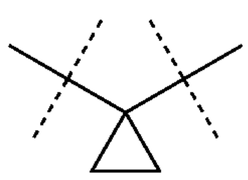
**[0106]** Embodiment 4. The compound of Embodiment 1 wherein $R^A$ is —$C(=O)NHSO_2R^B$ where $R^B$ is —$CH_3$.

**[0107]** Embodiment 5. The compound of Embodiment 1-4 wherein $R^C$ is —CN, —F, or —Cl.

**[0108]** Embodiment 6. The compound of Embodiment 1-5 wherein $R^C$ is —F or —Cl.

**[0109]** Embodiment 7. The compound of Embodiment 1-6 wherein $L^1$, when present, is a geminally substituted alkyl, cycloalkyl or heterocycloalkyl group,

**[0110]** Embodiment 8. The compound of Embodiments 7 wherein $L^1$ is



**[0111]** Embodiment 9. The compound of any one of Embodiments 1-8 wherein $R^F$ is —H.

**[0112]** Embodiment 10. The compound of any one of Embodiments 1-9 wherein $R^G$ is —$CH_3$.

**[0113]** Embodiment 11. The compound of any one of Embodiments 1-10 wherein CY is substituted or unsubstituted phenyl.

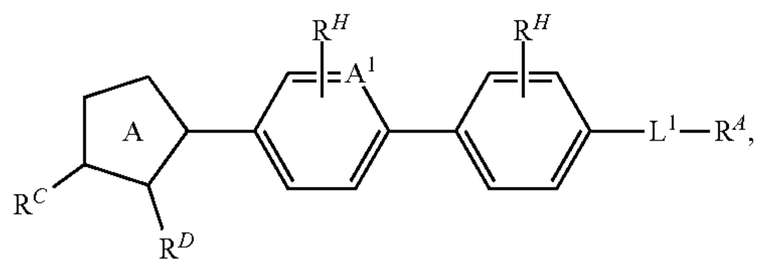
**[0114]** Embodiment 12. The compound of any one of Embodiments 1-11 wherein $R^H$ is —H, halogen, —CN, —$NO_2$, —OH, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ fluoroalkyl, $C_1$-$C_4$ fluoroalkoxy, and $C_1$-$C_4$ alkoxy.

**[0115]** Embodiment 13. The compound of any one of Embodiments 1-12 wherein $R^H$ are independently selected from —H, halogen or substituted or unsubstituted $C_1$-$C_4$ alkyl or substituted $C_1$-$C_4$ alkoxy.

**[0116]** Embodiment 14. The compound of any one of Embodiments 1-13 wherein $R^H$ is independently —H, —Cl, —F, —$CH_3$, —$CF_3$, —$OCH_3$ or —$OCF_3$.

**[0117]** Embodiment 15. A compound of Formula II having the structure:

Formula II

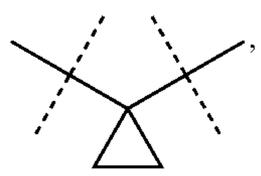



**[0118]** or a pharmaceutically acceptable salt or prodrug thereof,

**[0119]** wherein $R^A$ is —$CO_2H$, —$CO_2R^B$, tetrazolyl, —$C(=O)NH_2$, —CONHCN or $C(=O)NHSO_2R^B$;

**[0120]** $R^B$ is optionally substituted $C_1$-$C_4$ alkyl

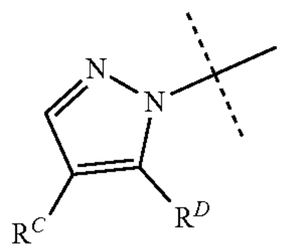
**[0121]** $L^1$ is optionally substituted $C_1$-$C_6$ alkylene; $C_1$-$C_6$ fluoroalkylene; or optionally substituted $C_1$-$C_6$ heteroalkylene or $L^1$ is



or disubstituted dimethylmethane.

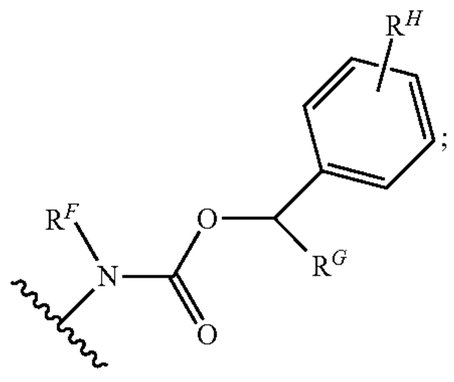
**[0122]** $A^1$ is =N— or =CH—;

**[0123]** Ring A has the structure:




**[0124]** $R^C$ is —ON, —F, —Cl, or $C_1$-$C_4$ fluoroalkyl;

**[0125]** $R^D$ is —$N(R^F)$—$C(=O)XCH(R^G)$—CY, wherein X is O and CY is phenyl substituted with one $R^H$:



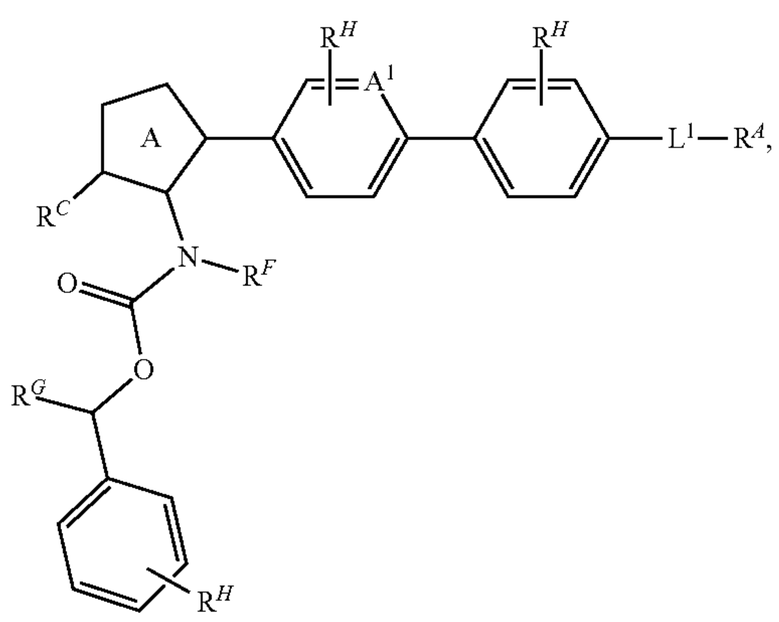

**[0126]** $R^E$, $R^F$ and $R^G$ independently are —H or $C_1$-$C_4$ alkyl or $C_3$-$C_6$ cycloalkyl or $R^E$ and $R^F$ independently are —H or $C_1$-$C_4$ alkyl or $C_1$-$C_6$ cycloalkyl and one $R^G$ is —$C_1$-$C_4$ alkyl and is taken together with the $R^H$ pheny moiety of the Ring A $R^D$ substituent and the carbon atom to which $R^G$ and said phenyl moiety is attached to define a substituted or unsubstituted carbocycle or a substituted or unsubstituted heterocycle;

**[0127]** $R^H$ is —H, halogen, —CN, —$NO_2$, —OH, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ fluoroalkyl, $C_1$-$C_4$ fluoroalkoxy, and $C_1$-$C_4$ alkoxy;

**[0128]** In particularly preferred Formula II compounds $R^A$ is —$CO_2H$, —CONHCN, —C(═O)$NHSO_2R^B$, or tetrazolyl, $R^B$ is $CH_3$, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC$(═O)$OCH(R^G)$—CY and $R^F$, $R^G$ and CY are as previously defined.

**[0129]** Embodiment 16. A compound of Formula III having the structure:

Formula III

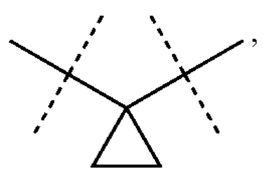


**[0130]** or a pharmaceutically acceptable salt or prodrug thereof,

**[0131]** wherein $R^A$ is —$CO_2H$, —CONHCN, tetrazolyl, or —C(═O)$NHSO_2R^B$;

**[0132]** $R^B$ is optionally substituted $C_1$-$C_4$ alkyl

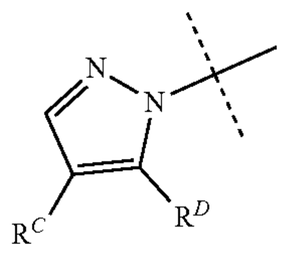
**[0133]** $L^1$ is substituted $C_1$-$C_6$ alkylene; $C_1$-$C_6$ fluoroalkylene; or optionally substituted $C_1$-$C_6$ heteroalkylene, or $L^1$, when present is



or disubstituted dimethylmethane.

**[0134]** $A^1$ is ═N— or ═CH—;

**[0135]** Ring A has the structure of one of:



**[0136]** $R^C$ is —CN, —F, or —Cl;

**[0137]** wherein CY is phenyl substituted with one $R^H$;

**[0138]** $R^F$ and $R^G$ independently are —H or $C_1$-$C_4$ alkyl or $C_3$-$C_6$ cycloalkyl or $R^F$ independently is —H or $C_1$-$C_4$ alkyl or $C_1$-$C_6$ cycloalkyl and one $R^G$ is —$C_1$-$C_4$ alkyl and is taken together with the $R^H$ pheny moiety of the Ring A $R^D$ substituent and the carbon atom to which $R^G$ and said phenyl moiety is attached to define a substituted or unsubstituted carbocycle or a substituted or unsubstituted heterocycle;

**[0139]** $R^H$ is —H, halogen, —CN, —$NO_2$, —OH, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ fluoroalkyl, $C_1$-$C_4$ fluoroalkoxy, and $C_1$-$C_4$ alkoxy;

**[0140]** Preferred Formula III compounds have $R^A$ is —$CO_2H$, —CONHCN, —C(═O)$NHSO_2R^B$, or tetrazolyl, $R^B$ is $CH_3$, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC$(═O)$OCH(R^G)$—CY and $R^F$ is —H, $R^G$ is —$CH_3$ and CY is as previously defined.

**[0141]** Embodiment 17. A composition comprising, essentially consisting of or consisting of one or more compounds of Formula I-III and one or more excipients.

**[0142]** In preferred embodiments the composition comprises, consists essentially of, or consists of one compound of Formula I-III and one or more excipients.

**[0143]** In other preferred embodiments the composition is a pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of one compound of Formula I-III and one or more pharmaceutically acceptable excipients.

**[0144]** Embodiment 18. A compound of Formula I-III or a pharmaceutically acceptable salt or prodrug thereof wherein the binding affinity of the compound to lysophosphatidic acid receptor-1 (LPA1R) is between about 10 μM and 1 pM or less

**[0145]** Embodiment 19. The compound of Embodiment 1-18 wherein the compound is a selective lysophosphatidic acid receptor-1 (LPA1R) compound.

**[0146]** Embodiment 20. A compound of Formula I-III or a pharmaceutically acceptable salt, or prodrug thereof wherein the compound is a selective lysophosphatidic acid receptor-1 (LPA1R) compound.

**[0147]** Embodiment 21. The compound of Embodiment 1-20 wherein the compound is a selective lysophosphatidic acid receptor-1 (LPA1R) compound wherein the binding affinity (i.e., $K_D$) of the LPA1R compound is between about 1 μM and 1 pM or less. In preferred Embodiments the $K_D$ is 100 nM or less, more preferably 10 nM or less.

**[0148]** Embodiment 22. A compound of Table 1.

**[0149]** Embodiment 23. The compound of Embodiment 22 wherein the compound is (R)-1-(4-(5-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(3-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, or (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate;

**[0150]** Embodiment 24. The compound of Embodiment 22 wherein the compound is (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-

(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-3-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, or (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid;

**[0151]** Embodiment 25. The compound of Embodiment 22 wherein the compound is (R)-1-{4'-[5-(1-Phenyl-ethoxy-carbonylamino)-4-trifluoromethyl-pyrazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid, or (R)-1-{2-Fluoro-4'-[5-(1-phenyl-ethoxycarbonylamino)-4-trifluoromethyl-pyrazol-1-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid;

**[0152]** Embodiment 26. The compound of Embodiment 22 wherein the compound is (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-2-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid, or (R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid;

**[0153]** Embodiment 27. The compound of Embodiment 22 wherein the compound is (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, or (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate;

**[0154]** Embodiment 28. The compound of Embodiment 22 wherein the compound is (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate;

**[0155]** Embodiment 29. The compound of Embodiment 22 wherein the compound is (R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate;

**[0156]** Embodiment 30. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Table 1 and one or more pharmaceutically acceptable excipients.

**[0157]** Embodiment 31. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Embodiment 23 and one or more pharmaceutically acceptable excipients.

**[0158]** Embodiment 32. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Embodiment 24 and one or more pharmaceutically acceptable excipients.

**[0159]** Embodiment 33. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Embodiment 25 and one or more pharmaceutically acceptable excipients.

**[0160]** Embodiment 34. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Embodiment 26 and one or more pharmaceutically acceptable excipients.

**[0161]** Embodiment 35. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Embodiment 27 and one or more pharmaceutically acceptable excipients.

**[0162]** Embodiment 36. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Embodiment 28 and one or more pharmaceutically acceptable excipients.

**[0163]** Embodiment 37. A pharmaceutically acceptable formulation comprising, consisting essentially of, or consisting of a compound of Embodiment 29 and one or more pharmaceutically acceptable excipients.

**[0164]** Embodiment 38. A method comprising administering an effective amount of a Formula I-III compound to a subject having a LPA-dependent or LPA-mediated disease or condition.

**[0165]** Embodiment 39. The method of Embodiment 38 wherein the LPA-dependent or LPA-mediated disease or condition is a disease with fibrosis of the organs.

**[0166]** Embodiment 40. The method of Embodiment 39 wherein the fibrosis is of the liver, kidney, lung, heart, eye and the like.

**[0167]** Embodiment 41. The method of Embodiment 38 wherein the LPA-dependent or LPA-mediated disease or condition is chronic pain

**[0168]** Embodiment 42. The method of Embodiment 38 wherein the LPA-dependent or LPA-mediated disease or condition is pruritus.

**[0169]** Embodiment 43. The method of Embodiment 38 wherein the LPA-mediated disease is a proliferative disease including cancer (solid tumor, solid tumor metastasis, vascular fibroma, myeloma, multiple myeloma, Kaposi's sarcoma, leukemia, chronic lymphocytic leukemia (CLL) and the like) and invasive metastasis of cancer cell, including ovarian, breast and triple negative breast cancer and the like,

**[0170]** Embodiment 44. The method of Embodiment 38 wherein the LPA-mediated disease is an inflammatory disease including psoriasis, nephropathy, pneumonia and the like,

**[0171]** Embodiment 45. The method of Embodiment 38 wherein the LPA-mediated disease is a gastrointestinal disease such as inflammatory bowel disease,

**[0172]** Embodiment 46. The method of Embodiment 38 wherein the LPA-mediated disease is an ocular disease including age-related macular degeneration (AMD), dia-

betic retinopathy, proliferative vitreoretinopathy (PVR), cicatricial pemphigoid, glaucoma filtration surgery scarring, uveitis and the like,

**[0173]** Embodiment 47. The method of Embodiment 38 wherein the LPA-mediated disease is a liver disease including acute hepatitis, chronic hepatitis, liver fibrosis, liver cirrhosis, cholestatic pruritus, portal hypertension, regenerative failure, nonalcoholic steatohepatitis (NASH), liver hypofunction, hepatic blood flow disorder, and the like,

**[0174]** Embodiment 48. The method of Embodiment 38 wherein the LPA-mediated disease is a renal disease including chronic kidney disease, end stage renal disease, uremic pruritus, nephropathy including diabetic nephropathy and the like,

**[0175]** Embodiment 49. The method of Embodiment 38 wherein the LPA-mediated disease is a skin disease including scleroderma, skin scarring, atopic dermatitis, psoriasis and the like,

**[0176]** Embodiment 50. The method of any one of Embodiments 38-49 wherein the subject is a human.

**[0177]** Embodiment 51. The method of any one of Embodiments 38-50 wherein the compound is selected from Table 1.

**[0178]** Embodiment 52. The method of any one of Embodiments 78-90 wherein the compound is (R)-1-(4-(5-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(3-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-3-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-2-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid, (R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid;

**[0179]** Embodiment 53. The method of any one of Embodiments 38-50 wherein the compound is selected from Embodiment 23.

**[0180]** Embodiment 54. The method of any one of Embodiments 38-50 wherein the compound is selected from Embodiment 24.

**[0181]** Embodiment 55. The method of any one of Embodiments 38-50 wherein the compound is selected from Embodiment 25.

**[0182]** Embodiment 56. The method of any one of Embodiments 38-50 wherein the compound is selected from Embodiment 26.

**[0183]** Embodiment 57. The method of any one of Embodiments 38-50 wherein the compound is selected from Embodiment 27.

**[0184]** Embodiment 58. The method of any one of Embodiments 38-50 wherein the compound is selected from Embodiment 28.

**[0185]** Embodiment 59. The method of any one of Embodiments 38-50 wherein the compound is selected from Embodiment 29.

**[0186]** Embodiment 60. A composition comprising, consisting essentially of or consisting of one or more compounds of Formula (I-III) and one or more agents currently used to treat a LPA-dependent or LPA-mediated disease or a disease or condition described herein.

**[0187]** Embodiment 61. A pharmaceutically acceptable formulation comprising, consisting essentially of or consisting of one or more compounds of Formula (I-III), one or more agents currently used to treat a LPA-dependent or LPA-mediated disease and one or more pharmaceutically acceptable excipients.

**[0188]** Embodiment 62. A method comprising administering in combination with or co-administrating a compound of Formula (I-III) to a subject with a LPA-dependent or LPA-

mediated disease or condition and a currently used agent to treat a LPA-dependent or LPA-mediated disease

**[0189]** The one or more additional therapeutically active agents other than compounds of Formula (I-III) are selected from: corticosteroids, immunosuppressants, analgesics, anticancer agents, anti-inflammatories, chemokine receptor antagonists, bronchodilators, leukotriene receptor antagonists, leukotriene formation inhibitors, platelet activating factor receptor antagonists, monoacylglycerol kinase inhibitors, phospholipase $A_1$ inhibitors, phospholipase $A_2$ inhibitors, and lysophospholipase D (lysoPLD) inhibitors, autotaxin inhibitors, decongestants, mast cell stabilizers, antihistamines, mucolytics, anticholinergics, antitussives, expectorants, and β-2 agonists.

**[0190]** In preferred embodiments the currently used agent (s) are selected from those described in the Merck Index known to affect lysophosphatidic acid receptor signaling. In other preferred embodiments the Formula (I-III) compound is selected from Table 1.

**[0191]** In other embodiments, therapies which combine a compound of Formula (I-III), with currently used agents that act on differing signalling pathways to the LPA synthesis or signalling pathway so as to provide complementary clinical outcomes, are encompassed herein for treating LPA-dependent or LPA-mediated diseases or conditions.

**[0192]** Examples of additional therapeutic agents include, but are not limited to, any of the following: gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib, geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, or PD 184352, Taxol™ (paclitaxel), and analogs of Taxol™, such as Taxotere™, U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600 125, BAY 43-9006, wortmannin, or LY294002, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amino glutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; deazaguanine; deazaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rlL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spiro germanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozotocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfm; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, mechloroethamine, cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine, hexamethylmelamine, thiotepa, busulfan), carmustine, lomusitne, semustine, streptozocin, ortriazenes, dacarbazine, methotrexate, fluorouracil, floxouridine, Cytarabine, mercaptopurine, thioguanine, pentostatin, hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate, estrogens, diethlystilbestrol, ethinyl estradiol, tamoxifen), testosterone propionate, fluoxymesterone, flutamide, leuprolide, cisplatin, carboblatin, mitoxantrone), procarbazine, mitotane, amino glutethimide, Erbulozole, Dolastatin 10, Mivobulin isethionate, Vincristine, NSC-639829, Discodermolide, ABT-751, Altorhyrtin A and Altorhyrtin C), Spongistatins 1-9, Cemadotin hydrochloride, Epothilone A, Epothilone B, Epothilone C, Epothilone D, Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone AN-oxide, 16-aza-epothilone B, 21aminoepothilone B, 21-hydroxyepothilone D, 26-fluoroepothilone, Auristatin PE, Soblidotin, Cryptophycin 52, Vitilevuamide, Tubulysin A, Canadensol, Centaureidin, Oncocidin Al Fijianolide B, Laulimalide, Narcosine, Nascapine, Hemiasterlin, Vanadocene acetylacetonate, Indanocine Eleutherobins (such as Desmethyleleutherobin, Desacetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, Diazonamide A, Taccalonolide A, Diozostatin, (−)-Phenylahistin, Myoseverin B, Resverastatin phosphate sodium, Aprepitant, cannabis, marinol, dronabinol, erythropoetin-α, Filgrastim, rituximab, natalizumab, cyclophosphamide, penicillamine, cyclosporine, nitrosoureas, cisplatin, carboplatin, oxaliplatin, methotrexate, azathioprine, mercaptopurine, pyrimidine analogues, protein synthesis inhibitors, dactinomycin, anthracyclines, mitomycin C, bleomycin, mithramycin, Atgam® Thymoglobuline®, OKT3®, basiliximab, daclizumab, cyclosporin,

tacrolimus, sirolimus, Interferons, opioids, infliximab, etanercept, adalimumab, golimumab, leflunomide, sulfasalazine, hydroxychloroquinine, minocycline, rapamicin, mycophenolic acid, mycophenolate mofetil, FTY720, Cyclosporin A (CsA) or tacrolimus (FK506), aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, valdecoxib, parecoxib, etoricoxib, lumiracoxib, betamethasone, prednisone, alclometasone, aldosterone, amcinonide, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, cortisone, cortivazol, deflazacort, deoxycorticosterone, desonide, desoximetasone, desoxycortone, dexamethasone, diflorasone, diflucortolone, difluprednate, fluclorolone, fludrocortisone, fludroxycortide, flumetasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, fluprednidene, fluticasone, formocorta1, halcinonide, halometasone, hydrocortisone/cortisol, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, lotepredno1, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, paramethasone, prednicarbate, prednisone/prednisolone, rimexolone, tixocortol, triamcinolone, ulobetasol, pioglitazone, clofibrate, fenofibrate gemfibrozil, folic acid, isbogrel, ozagrel, ridogrel, dazoxiben, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, nisvastatin, and rosuvastatin, edaravone, vitamin C, TROLOX™, citicoline and minicycline, (2R)-2-propyloctanoic acid, propranolol, nadolol, timolol, pindolol, labetalol, metoprolol, atenolol, esmolol and acebutolol, memantine, traxoprodil, tirofiban lamifiban, argatroban, enalapril, cyclandelate, losartan, valsartan, candesartan, irbesartan, telmisartan, olmesartan, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin etabonate, sotagliflozin, tofogliflozin, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, mepyramine (pyrilamine), antazoline, diphenhydramine, carbinoxamine, doxylamine, clemastine, dimenhydrinate, pheniramine, chlorphenamine (chlorpheniramine), dexchlorpheniramine, brompheniramine, triprolidine, cetirizine, cyclizine, chlorcyclizine, hydroxyzine, meclizine, loratadine, desloratidine, promethazine, alimemazine (trimeprazine), cyproheptadine, azatadine, ketotifen, acrivastine, astemizole, cetirizine, mizolastine, terfenadine, azelastine, epinastine, levocabastine, olopatadine, levocetirizine, fexofenadine, rupatadine, bepotastine), mucolytics, anticholinergics, antitussives, analgesics, expectorants, albuterol, ephedrine, epinephrine, fomoterol, metaproterenol, terbutaline, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone propionate, triamcinolone acetonide, ipratropium bromide, pseudoephedrine, theophylline, montelukast, pranlukast, tomelukast, zafirlukast, ambrisentan, bosentan, enrasentan, sitaxsentan, tezosentan, iloprost, treprostinil, pirfenidone, epinephrine, isoproterenol, orciprenaline, xanthines, zileuton.

**[0193]** Embodiment 63. The method of Embodiments 60-62 wherein the subject is a human.

**[0194]** Embodiment 64. The method of Embodiments 60-62 wherein the Formula I-III compound(s) are selected from Table 1.

**[0195]** Embodiment 65. The method of Embodiments 60-62 wherein the Formula I-III compound(s) are selected from the group consisting of (R)-1-(4-(5-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(3-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-3-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-bi-

phenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl) carbamate, (R)-2-(4'-(5-(((1-(2-chlorophenyl)ethoxy) carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid, (R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid;

**[0196]** Embodiment 66. The method of Embodiments 60-63 wherein the Formula I-III compound(s) are selected from Embodiment 23.

**[0197]** Embodiment 67. The method of Embodiments 60-63 wherein the Formula I-III compound(s) are selected from Embodiment 24.

**[0198]** Embodiment 68. The method of Embodiments 60-63 wherein the Formula I-III compound(s) are selected from Embodiment 25.

**[0199]** Embodiment 69. The method of Embodiment 60-63 wherein the Formula I-III compound(s) are selected from Embodiment 26.

**[0200]** Embodiment 70. The method of Embodiment 60-63 wherein the Formula I-III compound(s) are selected from Embodiment 27.

**[0201]** Embodiment 71. The method of Embodiment 60-63 wherein the Formula I-III compound(s) are selected from Embodiment 28.

**[0202]** Embodiment 72. The method of Embodiment 60-63 wherein the Formula I-III compound(s) are selected from Embodiment 29.

**[0203]** Embodiment 73. The composition of Embodiment 60 where the currently used agent is a mast cell stabilizing agent

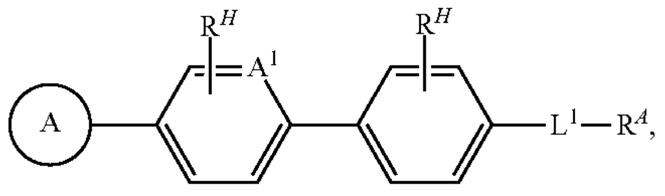
**[0204]** Embodiment 74. The composition of Embodiment 60 where the currently used agent is a platelet activating factor receptor antagonist,

**[0205]** Embodiment 75. The composition of Embodiment 73 where the mast cell stabilizing agent is cromoglicate, nedocromil, azelastine, bepotastine, epinastine, ketotifen, olopatadine and rupatadine.

**[0206]** Embodiment 76. The composition of Embodiment 74 where the platelet activating factor receptor antagonist is rupatadine, SM-12502, CV-3988 and WEB 2170.

**[0207]** Embodiment 1A. A compound wherein the compound has the structure of Formula I

Formula I



or a pharmaceutically acceptable salt or prodrug thereof,

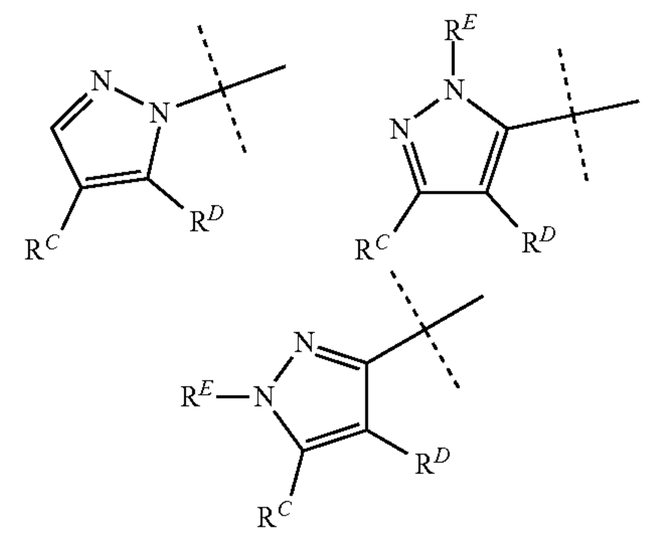
**[0208]** wherein $R^A$ is —$CO_2H$, —CONHCN, tetrazolyl, or C(═O)$NHSO_2R^B$;

**[0209]** wherein $R^B$ is substituted or unsubstituted $C_1$-$C_4$ alkyl;

**[0210]** $L^1$ is substituted or unsubstituted $C_1$-$C_6$ alkylene, substituted or unsubstituted $C_1$-$C_6$ fluoroalkylene, substituted or unsubstituted $C_3$-$C_8$ cycloalkylene, substituted or unsubstituted $C_1$-$C_6$ heteroalkylene;

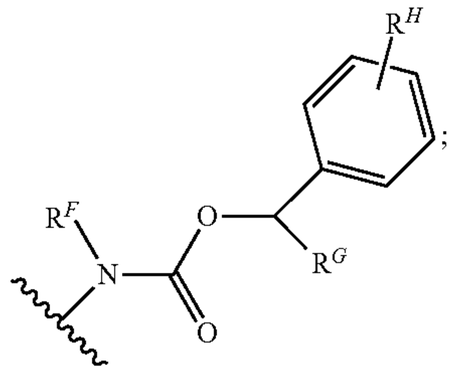
**[0211]** wherein A1 is —N═ or —CH;

**[0212]** wherein Ring A has the structure of one of



**[0213]** wherein $R^C$ is —CN, —F, —Cl, —Br, —I, —O$C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, or $C_1$-$C_4$ fluoroalkyl;

**[0214]** and $R^D$ is —N($R^F$)—C(═O)XCH($R^G$)—CY, wherein X is O and CY is phenyl substituted with one $R^H$:



**[0215]** $R^E$, $R^F$ and $R^G$ independently are —H or $C_1$-$C_4$ alkyl or $C_3$-$C_6$ cycloalkyl or $R^E$ and $R^F$ independently are —H or $C_1$-$C_4$ alkyl or $C_1$-$C_6$ cycloalkyl and one $R^G$ is —$C_1$-$C_4$ alkyl and is taken together with the $R^H$ pheny moiety of the Ring A $R^D$ substituent and the carbon atom to which $R^G$ and said phenyl moiety is attached to define a substituted or unsubstituted carbocycle or a substituted or unsubstituted heterocycle;

**[0216]** $R^H$ is independently —H, halogen, —CN, —$NO_2$, —OH, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ fluoroalkyl, $C_1$-$C_4$ fluoroalkoxy, or $C_1$-$C_4$ alkoxy,

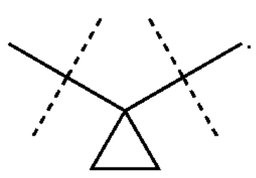
**[0217]** In some embodiments $R^C$ is —CN, —F, —Cl, —Br, —I, —O$C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, or $C_1$-$C_4$ fluoroalkyl and $R^D$ is —N($R^F$)—C(═O)OCH($R^G$)—CY,
wherein $R^F$ and each $R^G$ independently are —H or $C_1$-$C_4$ alkyl.

**[0218]** In preferred embodiments $R^A$ is —$CO_2H$, —CONHCN, tetrazolyl, or —C(═O)$NHSO_2R^B$, wherein $R^B$ is substituted or unsubstituted $C_1$-$C_4$ alkyl.

**[0219]** In particularly preferred embodiments $R^A$ is —$CO_2H$, —CONHCN, tetrazolyl, or —C(═O)$NHSO_2R^B$, wherein $R^B$ is —$CH_3$.

**[0220]** In some embodiments $L^1$ is substituted or unsubstituted $C_1$-$C_6$ alkylene, $C_1$-$C_6$ fluoroalkylene, or substituted or unsubstituted $C_1$-$C_6$ heteroalkylene.

**[0221]** In particularly preferred embodiments $L^1$ is



**[0222]** In some embodiments, Formula I compounds have $R^C$ defined as —CN, —F, —Cl, or $C_1$-$C_4$ fluoroalkyl.

**[0223]** In more preferred embodiments, Formula I compounds have $R^C$ defined as —F, or —Cl.

**[0224]** In some embodiments, Formula I compounds have $R^D$ defined as —$N(R^F)C(=O)$—$OCH(R^G)$—CY, wherein $R^F$ is —H or $C_1$-$C_4$ alkyl and X, CY and $R^G$ are as previously defined.

**[0225]** In more preferred embodiments, Formula I compounds have $R^D$ defined as —$N(R^F)C(=O)OCH(R^G)$—CY, wherein $R^F$ is —H and CY and $R^G$ are as previously defined.

**[0226]** In some embodiments, Formula I compounds have $R^F$ defined as H, $C_1$-$C_4$ alkyl or $C_3$-$C_6$ cycloalkyl.

**[0227]** In more preferred embodiments, Formula I compounds have $R^F$ defined as —H.

**[0228]** In some embodiments of Formula I compounds $R^G$ is independently —H or $C_1$-$C_4$ alkyl.

**[0229]** In more preferred embodiments, Formula I compounds have $R^G$ defined as —$CH_3$.

**[0230]** In some embodiments of Formula I compounds CY is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein if CY is substituted then CY is substituted with 1, 2, or 3 independently selected $R^H$.

**[0231]** In preferred Formula I compounds have $R^A$ is —$CO_2H$, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^F$, $R^G$, and CY are as previously defined.

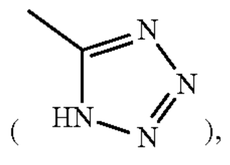
**[0232]** In other preferred Formula I compounds have $R^A$ is tetrazolyl, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^F$, $R^G$, and CY are as previously defined.

**[0233]** In other preferred Formula I compounds have $R^A$ is —$C(=O)NHSO_2R^B$, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^B$, $R^F$, $R^G$, and CY are as previously defined.

**[0234]** In other preferred Formula I compounds $R^A$ is —CONHCN, $R^C$ is —F or —Cl, $R^D$ is —$NR^FC(=O)OCH(R^G)$—CY, and $R^F$, $R^G$, and CY are as previously defined.

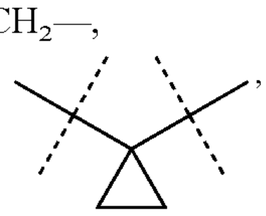
**[0235]** Embodiment 2A. The compound of Embodiment 1A, wherein:

**[0236]** $R^A$ is —$CO_2H$, tetrazolyl



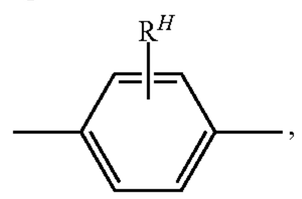
—$C(=O)NH_2$, or —$C(=O)NHSO_2R^B$;

**[0237]** $L^1$ is —$CH_2$—,



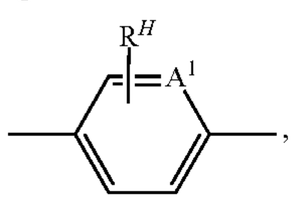
or disubstituted dimethylmethane;

**[0238]** in the ring



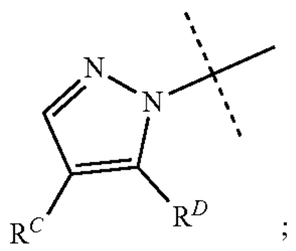
$R^H$ is —H, a halogen, or —$CH_3$;

**[0239]** in the ring



$A^1$ is CH or N and $R^H$ is —H;

**[0240]** Ring A has the structure of



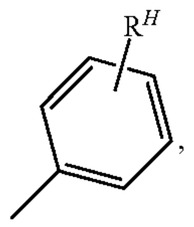
;

**[0241]** $R^C$ is —F, —Cl, —CN, or —$CF_3$;

**[0242]** $R^F$ is —H;

**[0243]** $R^G$ is —$CH_3$ in an R configuration; and

**[0244]** in the CY ring

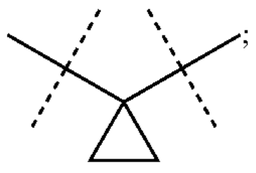


$R^H$ is —H or a halogen.

**[0245]** Embodiment 3A. The compound of Embodiment 2A, wherein:

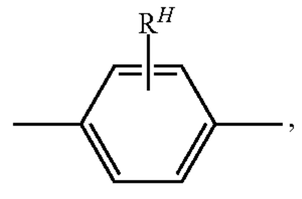
**[0246]** $R^A$ is $CO_2H$;

**[0247]** $L^1$ is



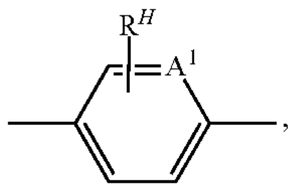
;

**[0248]** in the ring



$R^H$ is —H;

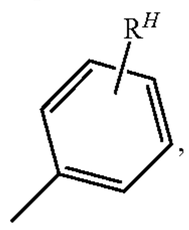
**[0249]** in the ring



$A^1$ is N and $R^H$ is —H;

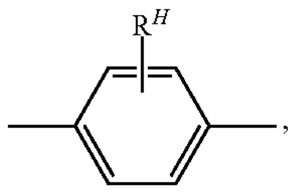
**[0250]** $R^C$ is —F; and

**[0251]** in the CY ring

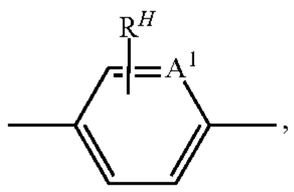


$R^H$ is —Cl.

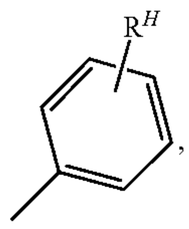
**[0252]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

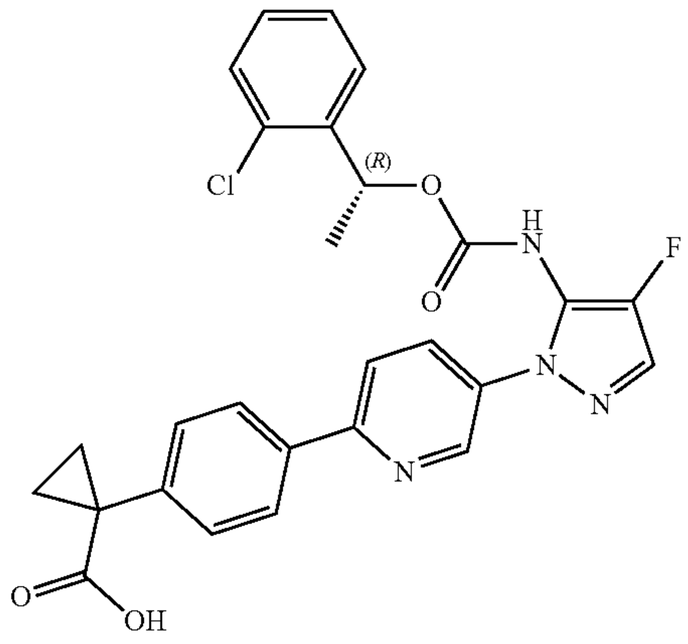


and the CY ring



individually. An exemplary molecule with this structure is Compound 1, (R)-1-(4-(5-(5-(((1-(2-chlorophenyl)ethoxy) carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)pyridin-2-yl) phenyl)cyclopropane-1-carboxylic acid.

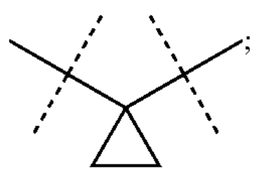
Compound 1



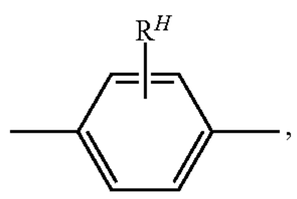
**[0253]** Embodiment 4A. The compound of Embodiment 2A, wherein:

**[0254]** $R^A$ is $CO_2H$;

**[0255]** $L^1$ is

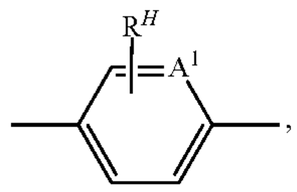


**[0256]** in the ring



$R^H$ is —H;

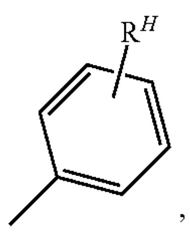
**[0257]** in the ring



$A^1$ is N and $R^H$ is —H;

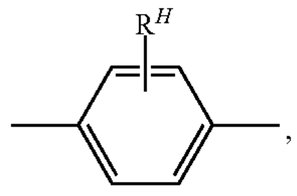
**[0258]** $R^C$ is —Cl; and

**[0259]** in the CY ring

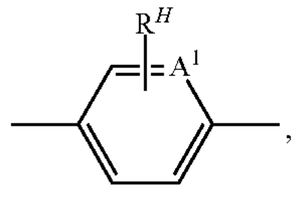


$R^H$ is —Cl.

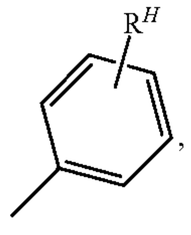
**[0260]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

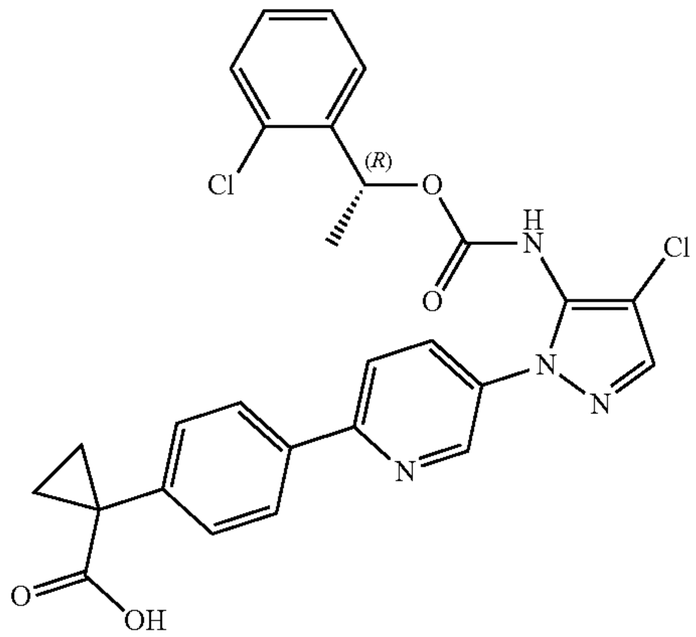


and the CY ring



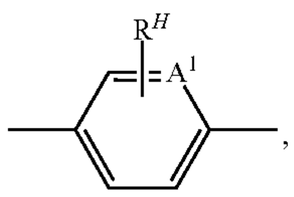
individually. An exemplary molecule with this structure is Compound 2, (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid.

Compound 2



**[0261]** Embodiment 5A. The compound of Embodiment 2A, wherein

**[0262]** in the ring

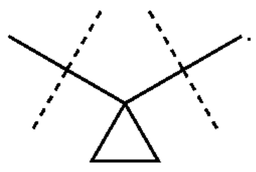


$A^1$ is CH and $R^H$ is —H.

**[0263]** Embodiment 6A. The compound of Embodiment 5A, wherein:

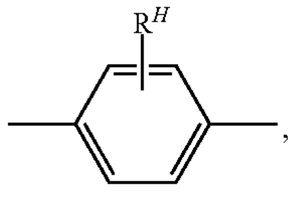
**[0264]** $R^A$ is $CO_2H$; and

**[0265]** $L^1$ is



**[0266]** Embodiment 7A. The compound of Embodiment 6A, wherein:

**[0267]** in the ring

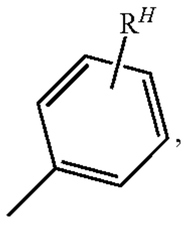


$R^H$ is —H.

**[0268]** Embodiment 8A. The compound of Embodiment 7A, wherein

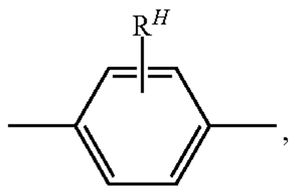
**[0269]** $R^C$ is —F; and

**[0270]** in the CY ring

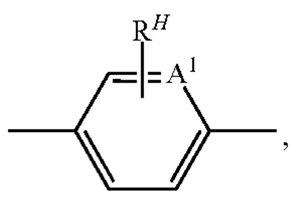


$R^H$ is —H.

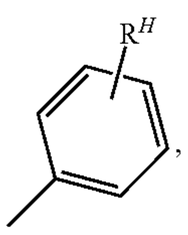
**[0271]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

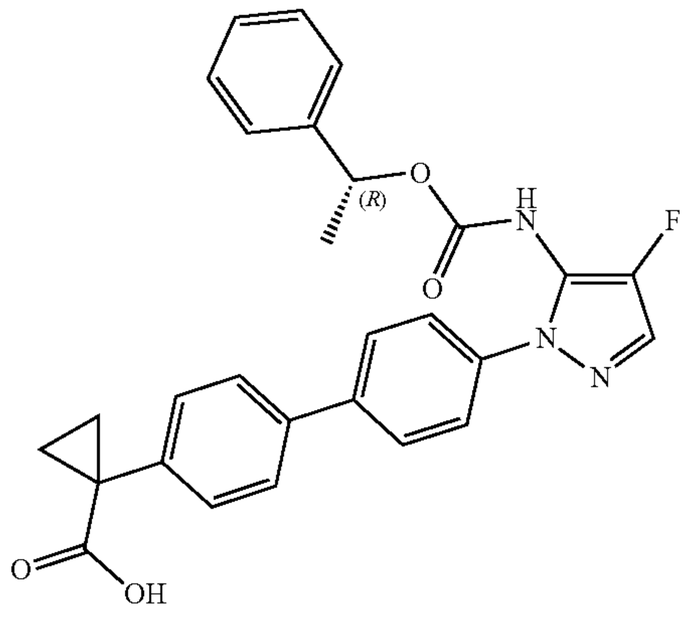


and the CY ring



individually. An exemplary molecule with this structure is Compound 3, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

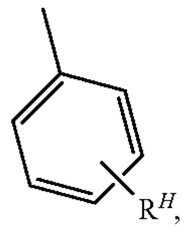
Compound 3



**[0272]** Embodiment 9A. The compound of Embodiment 7A, wherein:

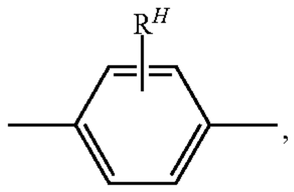
**[0273]** $R^C$ is —Cl; and

**[0274]** in the ring

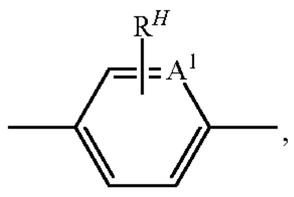


$R^H$ is —H.

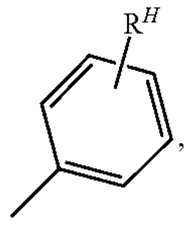
**[0275]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring



and the CY ring



individually. An exemplary molecule with this structure is Compound 4, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

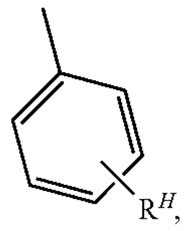
Compound 4



**[0276]** Embodiment 10A. The compound of Embodiment 7A, wherein:

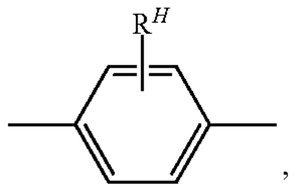
**[0277]** $R^C$ is —CN; and

**[0278]** in the ring

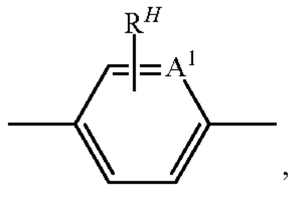


$R^H$ is —H.

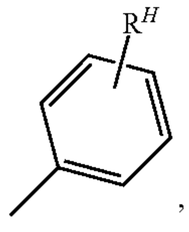
**[0279]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring



and the CY ring



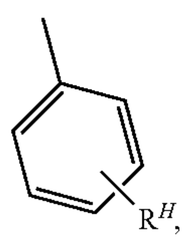
individually. An exemplary molecule with this structure is Compound 5, (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

Compound 5

**[0280]** Embodiment 11A. The compound of Embodiment 7A, wherein:

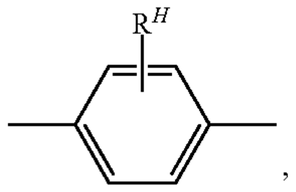
**[0281]** $R^C$ is —CN; and

**[0282]** in the ring

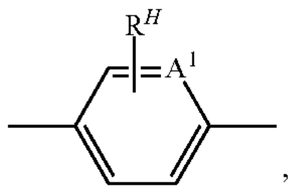


$R^H$ is —Cl.

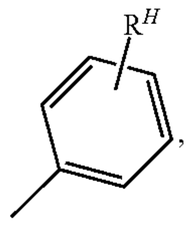
**[0283]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

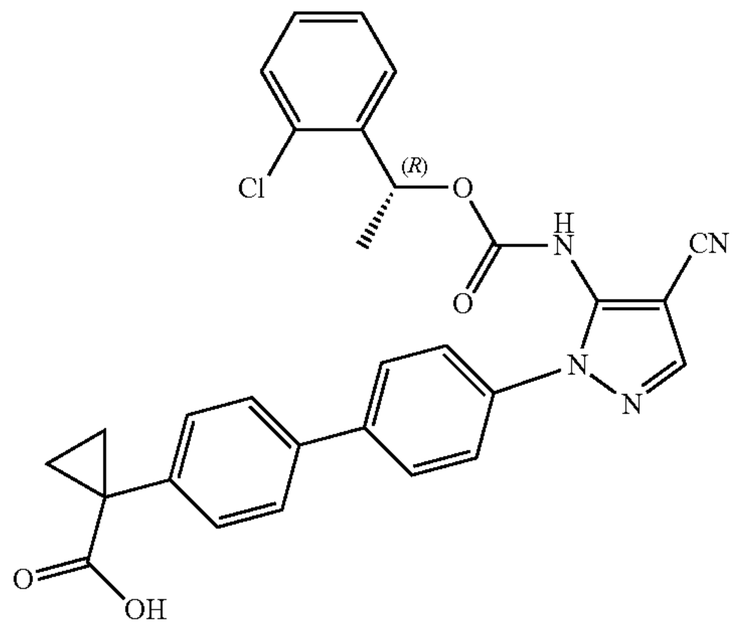


and the CY ring



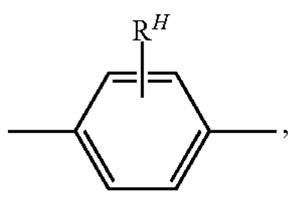
individually. An exemplary molecule with this structure is Compound 6, (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

Compound 6



**[0284]** Embodiment 12A. The compound of Embodiment 6A, wherein:

**[0285]** in the ring

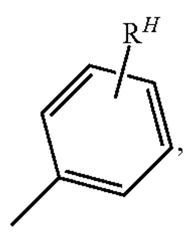


$R^H$ is —F.

**[0286]** Embodiment 13A. The compound of Embodiment 12A, wherein:

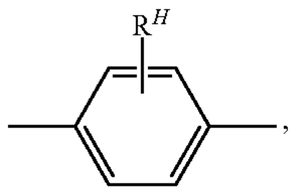
**[0287]** $R^C$ is —F; and

**[0288]** in the CY ring

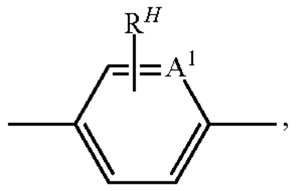


$R^H$ is —H.

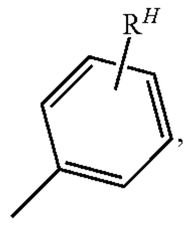
**[0289]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

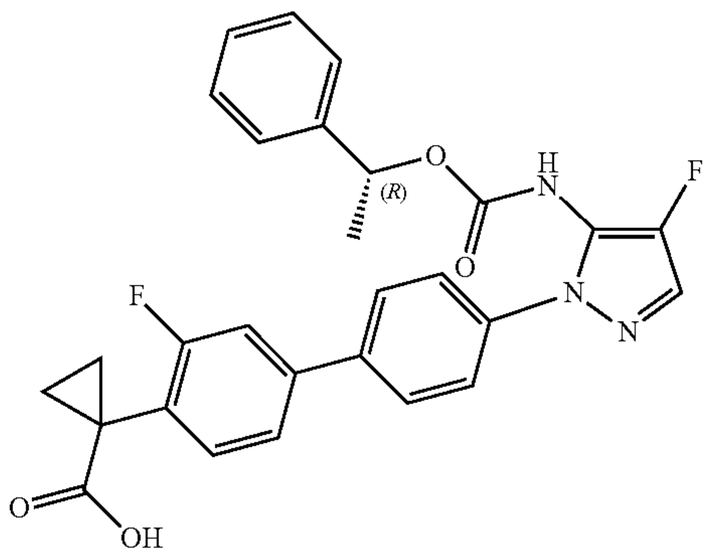


and the CY ring



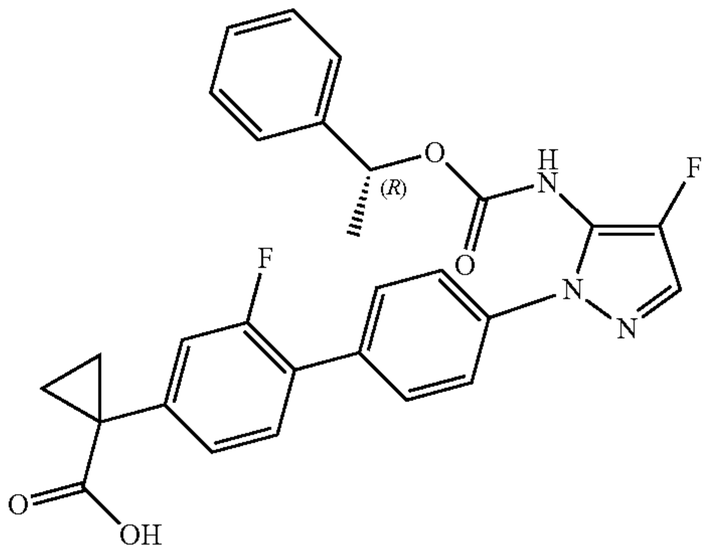
individually. Exemplary molecules with this structure are Compound 7, (R)-1-(3-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, and Compound 8, (R)-1-(2-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

Compound 7



-continued

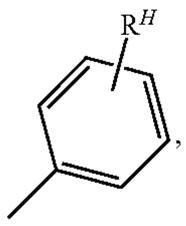
Compound 8



**[0290]** Embodiment 14A. The compound of Embodiment 12A, wherein:

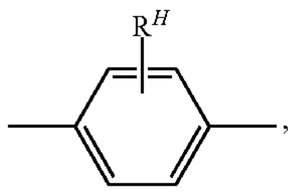
**[0291]** $R^C$ is —Cl; and

**[0292]** in the CY ring

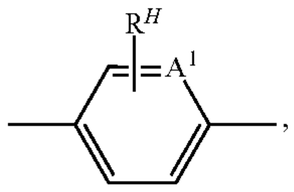


$R^H$ is —H.

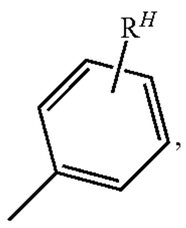
**[0293]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

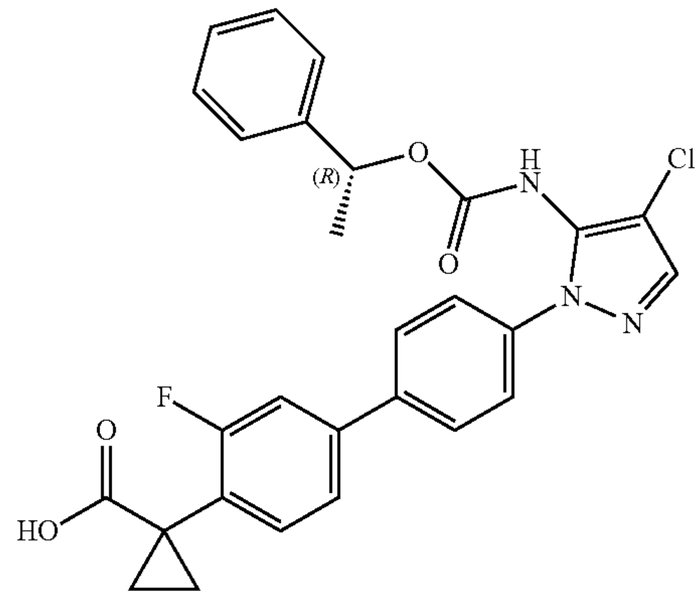


and the CY ring

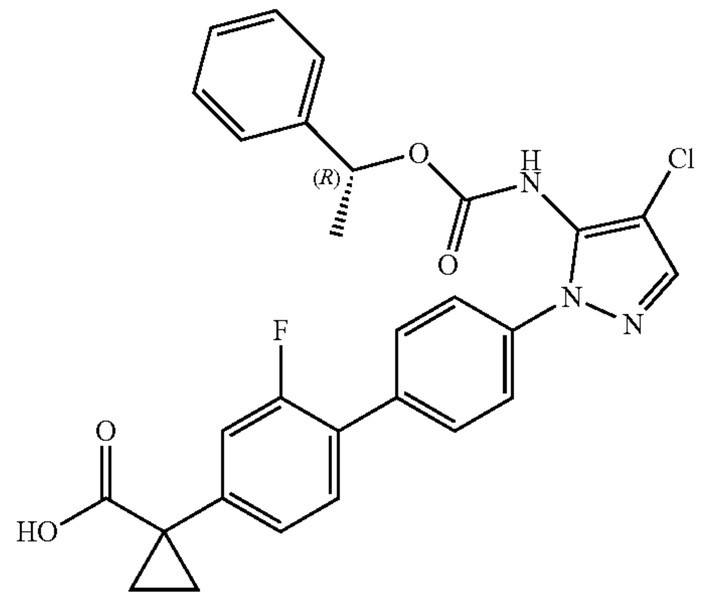


individually. Exemplary molecules with this structure are Compound 9, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-3-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, and Compound 10, R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

Compound 9

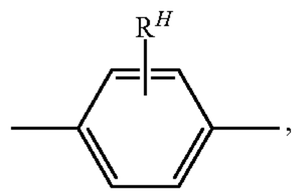


Compound 10



**[0294]** Embodiment 15A. The compound of Embodiment 6A, wherein:

**[0295]** in the ring

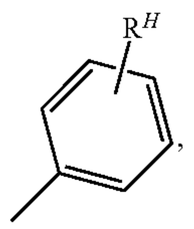


$R^H$ is —Cl.

**[0296]** Embodiment 16A. The compound of Embodiment 15A, wherein:

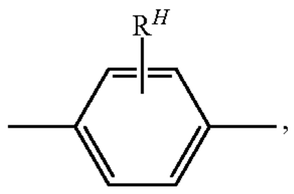
**[0297]** $R^C$ is —F; and

**[0298]** in the CY ring

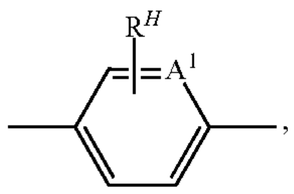


$R^H$ is —H.

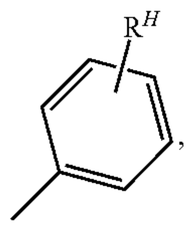
**[0299]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

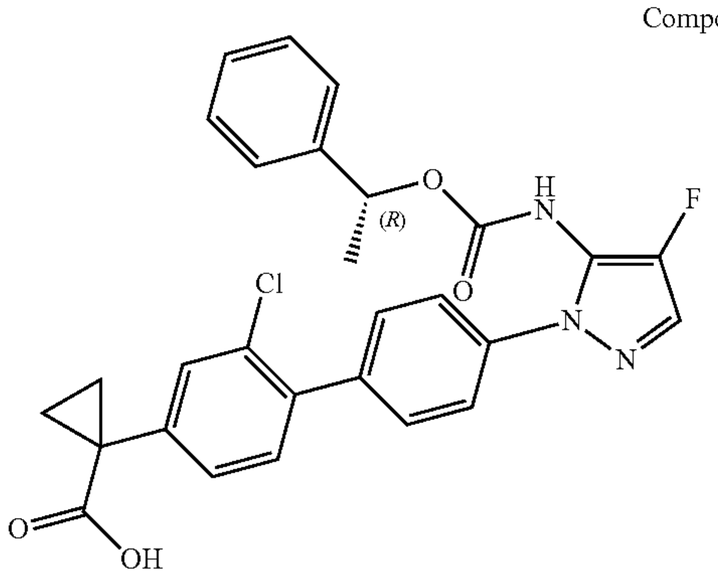


and the CY ring



individually. An exemplary molecule with this structure is Compound 11, (R)-1-(2-chloro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

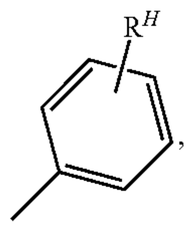
Compound 11



**[0300]** Embodiment 17A. The compound of Embodiment 15A, wherein:

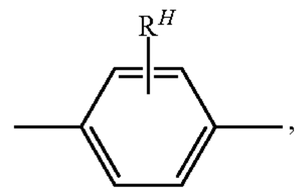
**[0301]** $R^C$ is —Cl; and

**[0302]** in the CY ring

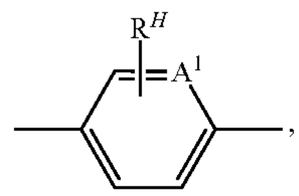


$R^H$ is —H.

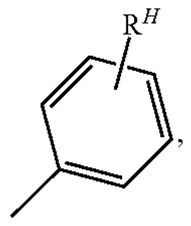
**[0303]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

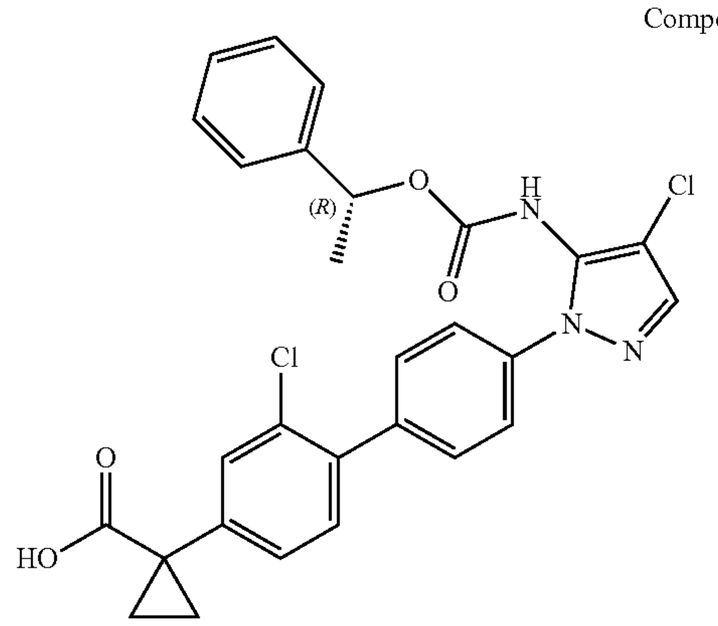


and the CY ring



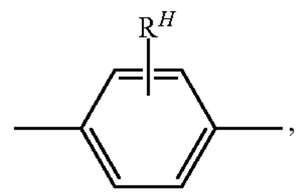
individually. An exemplary molecule with this structure is Compound 12, (R)-1-(2-chloro-4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

Compound 12



**[0304]** Embodiment 18A. The compound of Embodiment 6A, wherein:

**[0305]** in the ring

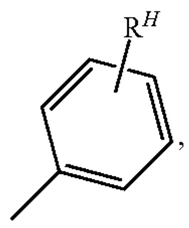


$R^H$ is —$CH_3$.

**[0306]** Embodiment 19A. The compound of Embodiment 18A, wherein:

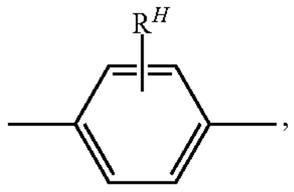
**[0307]** $R^C$ is —F; and,

**[0308]** in the CY ring

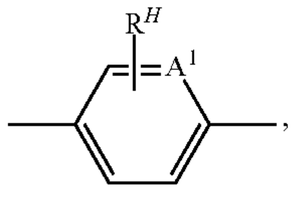


$R^H$ is —H.

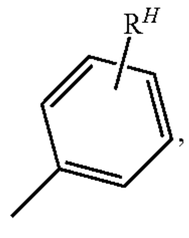
**[0309]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring



and the CY ring

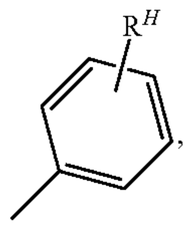


individually. An exemplary molecule with this structure is Compound 13, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

**[0310]** Embodiment 20A. The compound of Embodiment 18A, wherein:

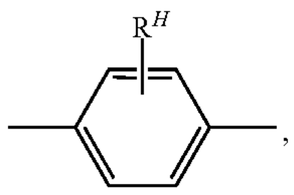
**[0311]** $R^C$ is —Cl; and

**[0312]** in the CY ring

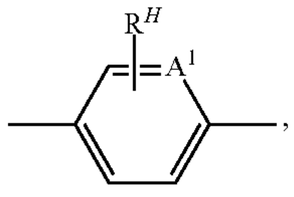


$R^H$ is —H.

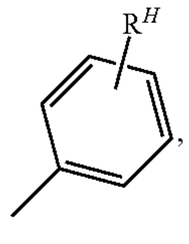
**[0313]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

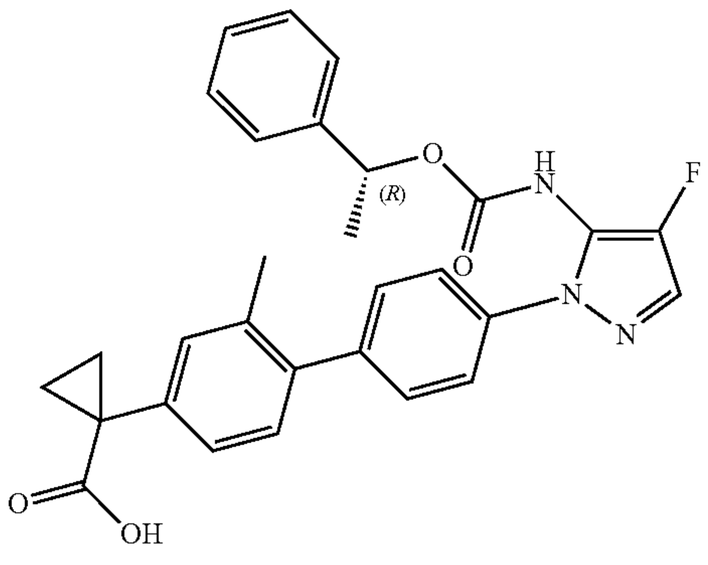


and the CY ring

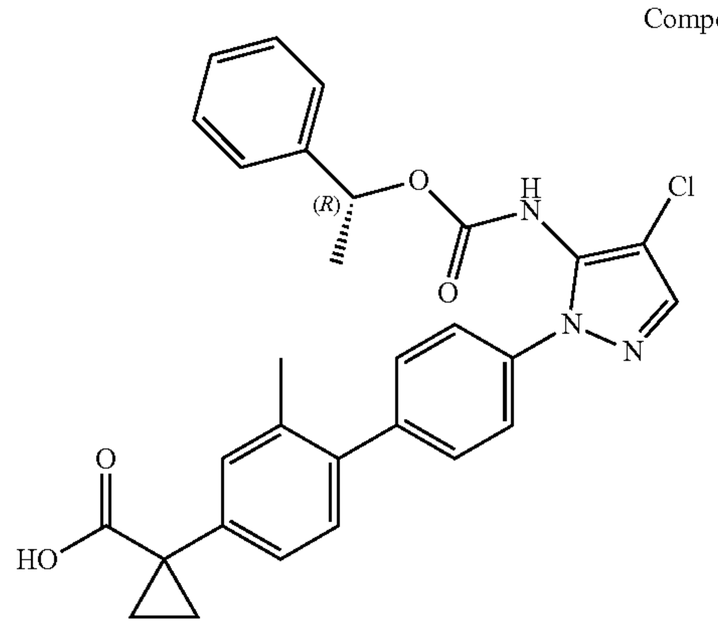


individually. An exemplary molecule with this structure is Compound 14, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid.

Compound 13



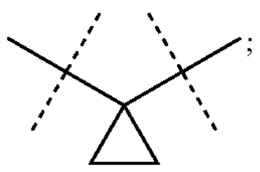
Compound 14



**[0314]** Embodiment 21A. The compound of Embodiment 5A, wherein:

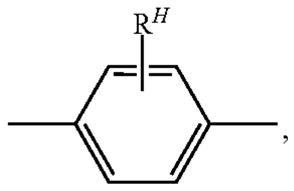
**[0315]** $R^A$ is —C(═O)$NH_2$;

**[0316]** $L^1$ is



;

**[0317]** in the ring

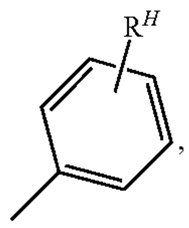


,

$R^H$ is —H;

**[0318]** $R^C$ is —F; and

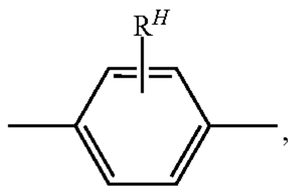
**[0319]** in the CY ring



,

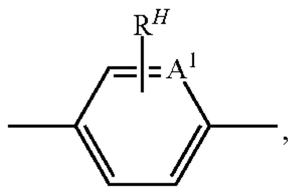
$R^H$ is —Cl.

**[0320]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



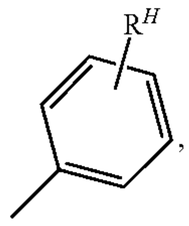
,

the ring



,

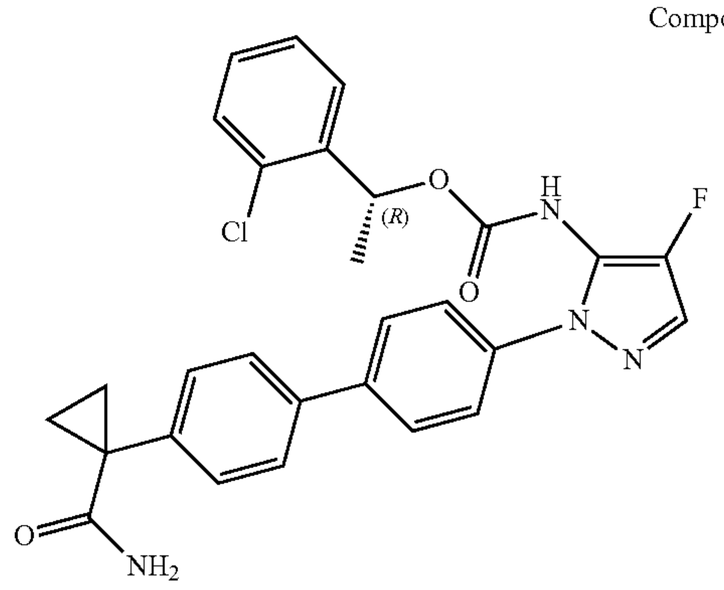
and the CY ring



,

individually. An exemplary molecule with this structure is Compound 15, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate.

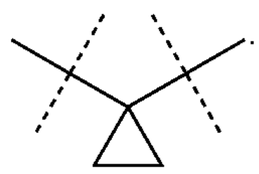
Compound 15



**[0321]** Embodiment 22A. The compound of Embodiment 5A, wherein:

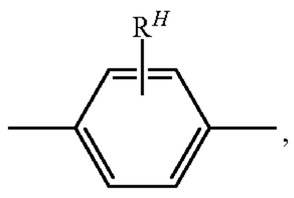
**[0322]** $R^A$ is —C(═O)$NHSO_2R^B$, where $R^B$ is —$CH_3$; and

**[0323]** $L^1$ is



**[0324]** Embodiment 23A. The compound of Embodiment 22A, wherein:

**[0325]** in the ring



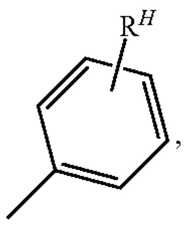
,

$R^H$ is —F.

**[0326]** Embodiment 24A. The compound of Embodiment 23A, wherein:

**[0327]** $R^C$ is —F; and

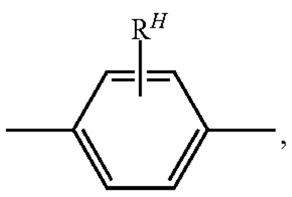
**[0328]** in the CY ring



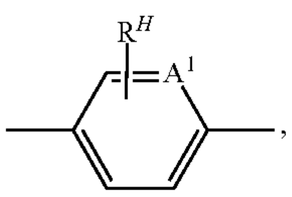
,

$R^H$ is —Cl.

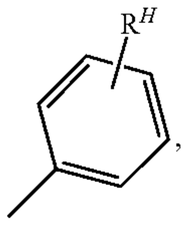
**[0329]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

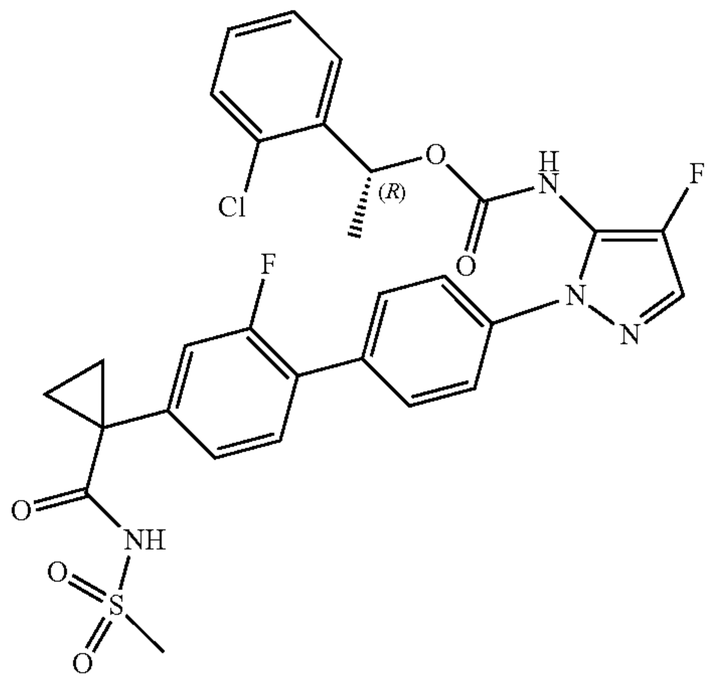


and the CY ring



individually. An exemplary molecule with this structure is Compound 16, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

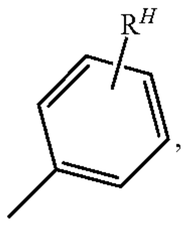
Compound 16



**[0330]** Embodiment 25A. The compound of Embodiment 23A, wherein:

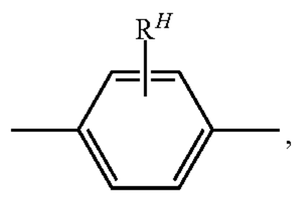
**[0331]** $R^C$ is —F; and

**[0332]** in the CY ring

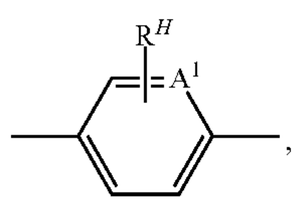


$R^H$ is —H.

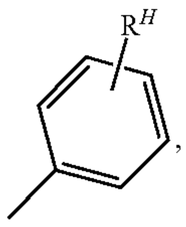
**[0333]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

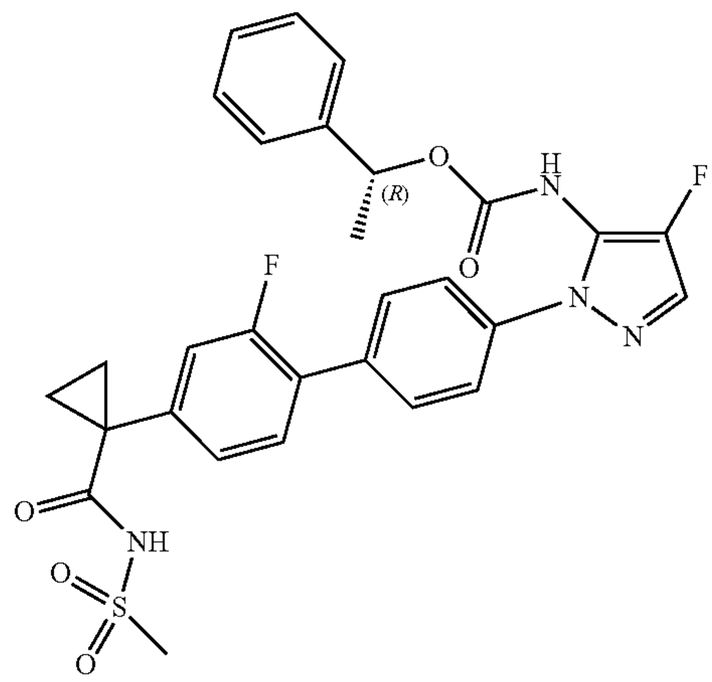


and the CY ring



individually. An exemplary molecule with this structure is Compound 17, (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

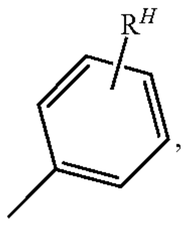
Compound 17



**[0334]** Embodiment 26A. The compound of Embodiment 23A, wherein:

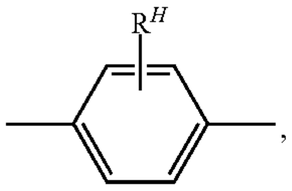
**[0335]** $R^C$ is —Cl; and

**[0336]** in the CY ring

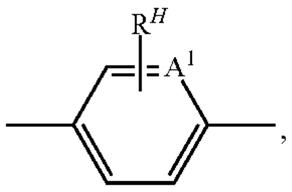


$R^H$ is —Cl.

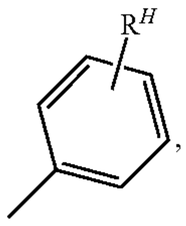
**[0337]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

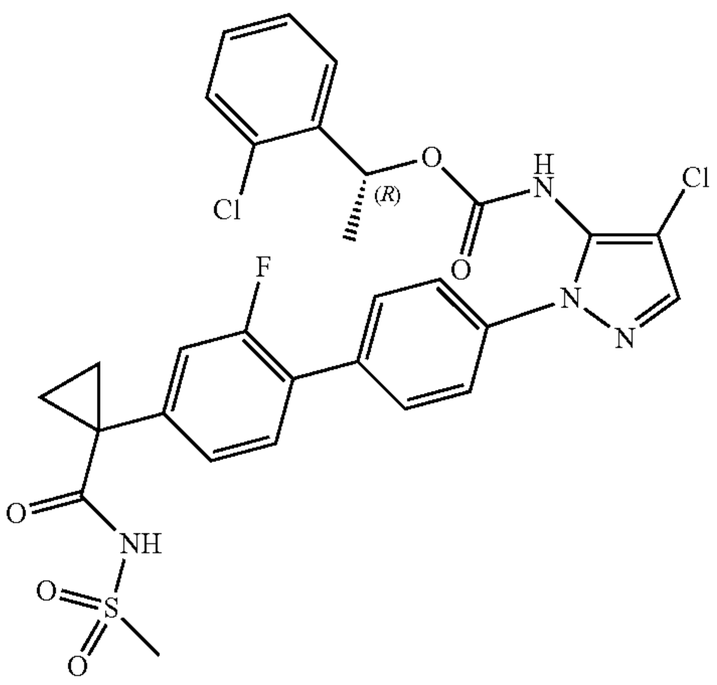


and the CY ring



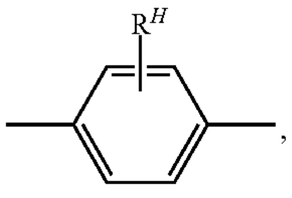
individually. An exemplary molecule with this structure is Compound 18, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

Compound 18



**[0338]** Embodiment 27A. The compound of Embodiment 22A, wherein:

**[0339]** in the ring

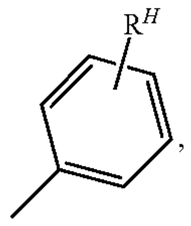


$R^H$ is —H.

**[0340]** Embodiment 28A. The compound of Embodiment 27A, wherein:

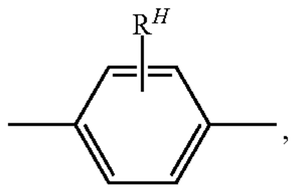
**[0341]** $R^C$ is —Cl; and

**[0342]** in the CY ring

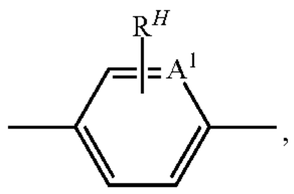


$R^H$ is —H.

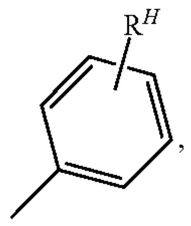
**[0343]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring



and the CY ring



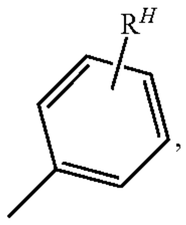
individually. An exemplary molecule with this structure is Compound 27, (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

Compound 19

**3[0344]** Embodiment 29A. The compound of Embodiment 27A, wherein:

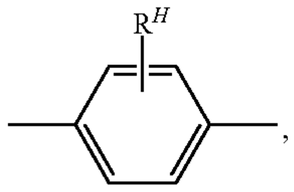
**[0345]** $R^C$ is —F; and

**[0346]** in the CY ring

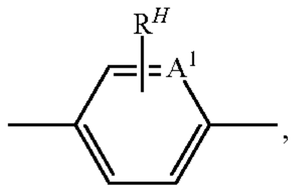


$R^H$ is —Cl.

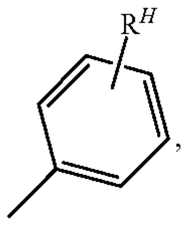
**[0347]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

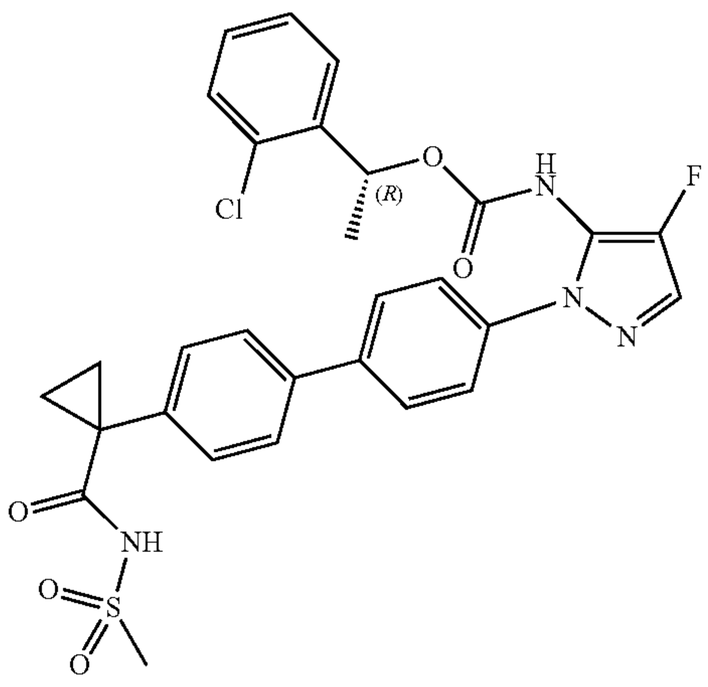


and the CY ring



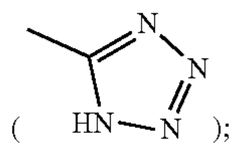
individually. An exemplary molecule with this structure is Compound 20, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

Compound 20

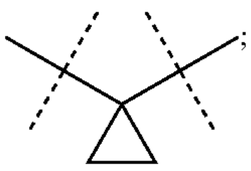


**[0348]** Embodiment 30A. The compound of Embodiment 5A, wherein:

**[0349]** $R^A$ is tetrazolyl

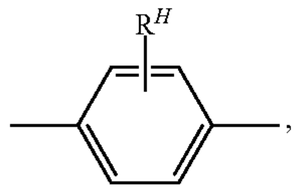


**[0350]** $L^1$ is



and

**[0351]** in the ring

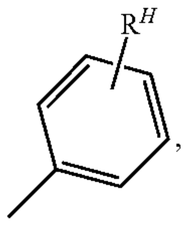


$R^H$ is —H.

**[0352]** Embodiment 31A. The compound of Embodiment 30A, wherein:

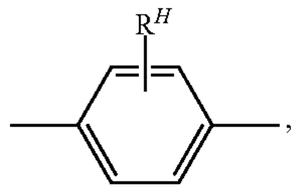
**[0353]** $R^C$ is —F; and

**[0354]** in the CY ring

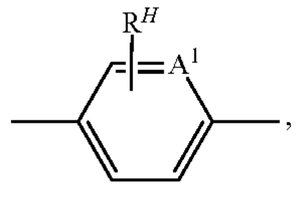


$R^H$ is —Cl.

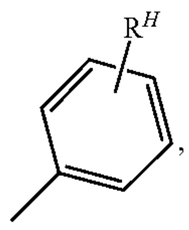
**[0355]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

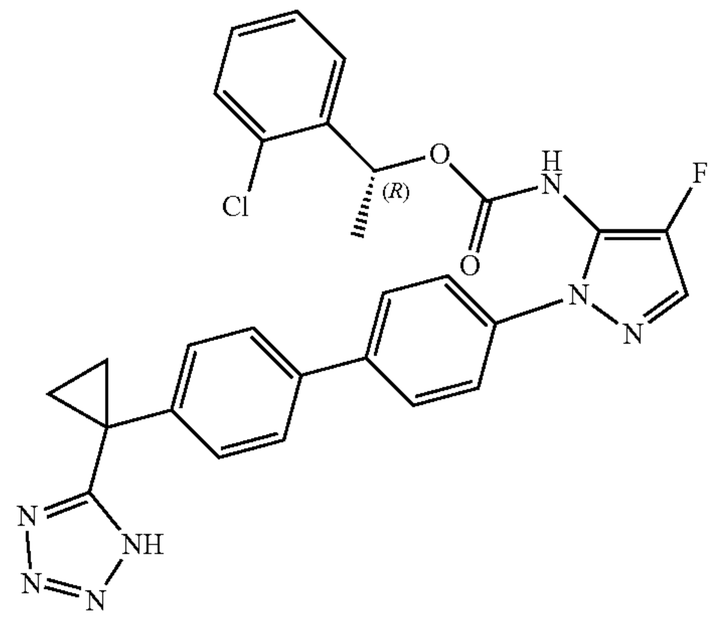


and the CY ring



individually. An exemplary molecule with this structure is Compound 21, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate.

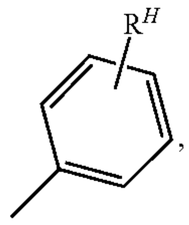
Compound 21



**[0356]** Embodiment 32A. The compound of Embodiment 30A, wherein:

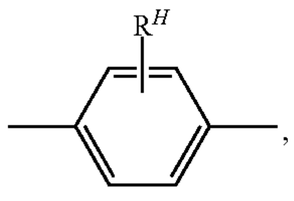
**[0357]** $R^C$ is —Cl; and

**[0358]** in the CY ring

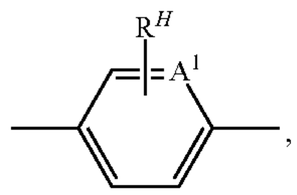


$R^H$ is —H.

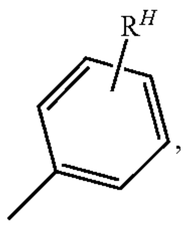
**[0359]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

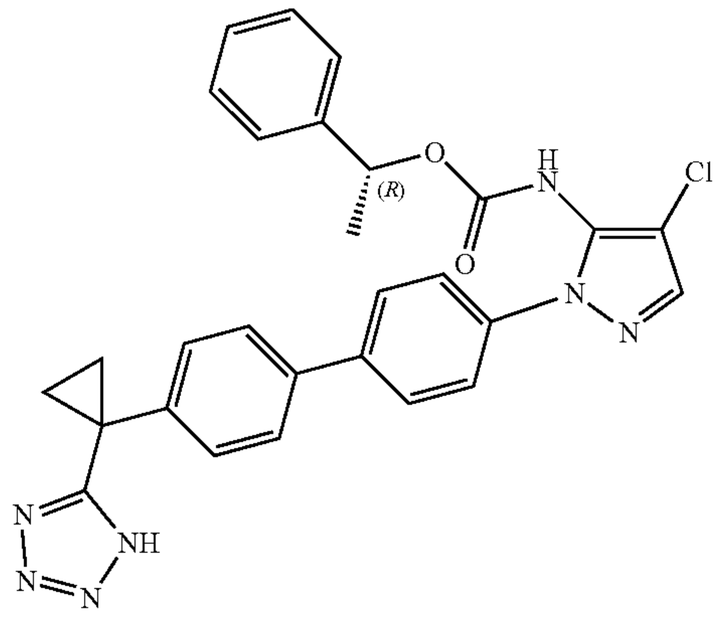


and the CY ring



individually. An exemplary molecule with this structure is Compound 22, (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate.

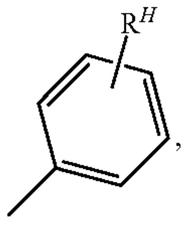
Compound 22



**[0360]** Embodiment 33A. The compound of Embodiment 30A, wherein:

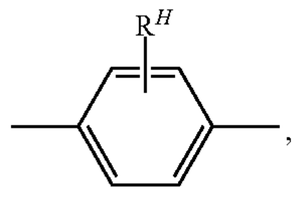
**[0361]** $R^C$ is —Cl; and

**[0362]** in the CY ring

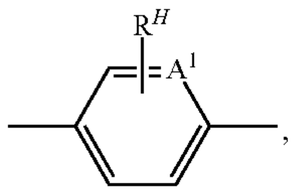


$R^H$ is —Cl.

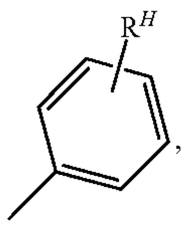
**[0363]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

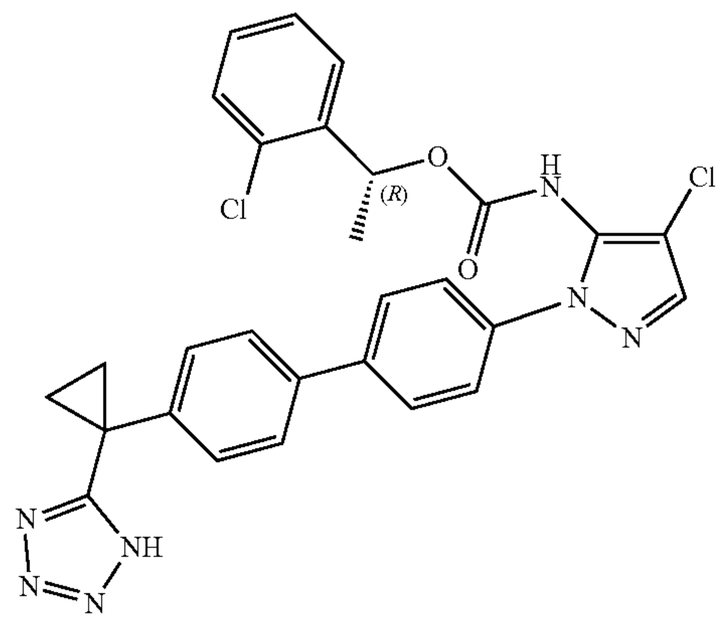


and the CY ring



individually. An exemplary molecule with this structure is Compound 23, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate.

Compound 23



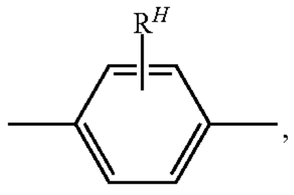
**[0364]** Embodiment 34A. The compound of Embodiment 5A, wherein:

**[0365]** $R^A$ is CONHCN

**[0366]** $L^1$ is

and

**[0367]** in the ring

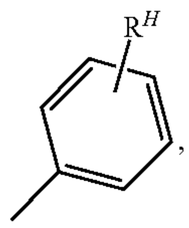


$R^H$ is —H.

**[0368]** Embodiment 35A. The compound of Embodiment 34A, wherein:

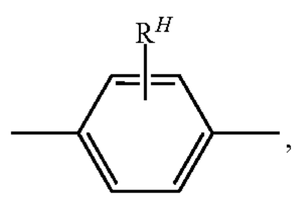
**[0369]** $R^C$ is —Cl; and

**[0370]** in the CY ring

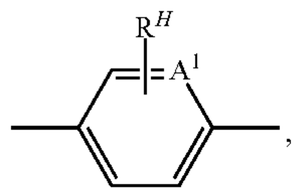


$R^H$ is —H.

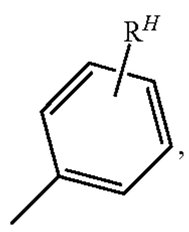
**[0371]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

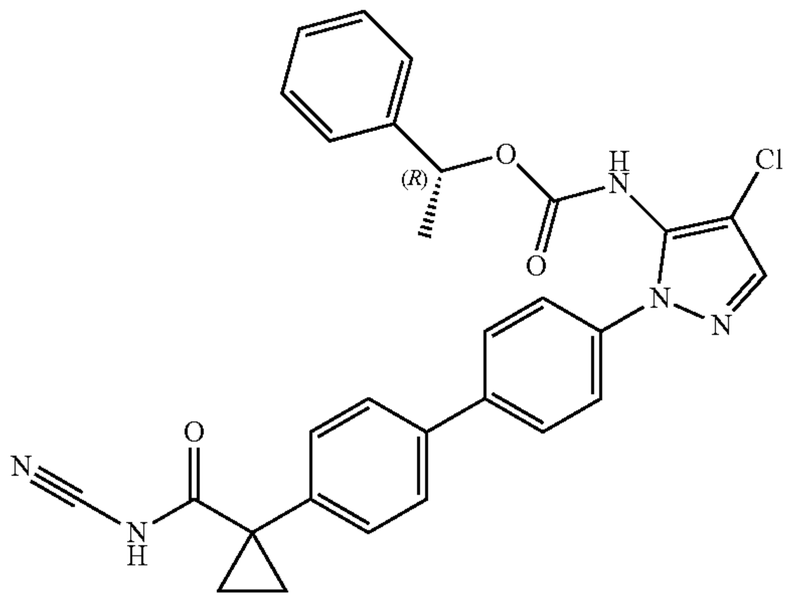


and the CY ring



individually. An exemplary molecule with this structure is Compound 24(R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

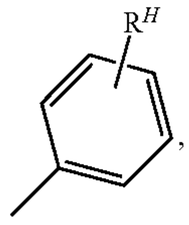
Compound 24



**[0372]** Embodiment 36A. The compound of Embodiment 33A, wherein:

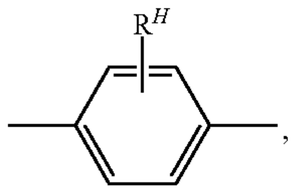
**[0373]** $R^C$ is —Cl; and

**[0374]** in the CY ring

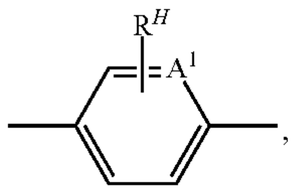


$R^H$ is —Cl.

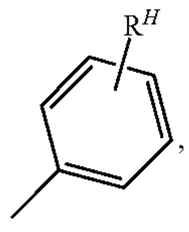
**[0375]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

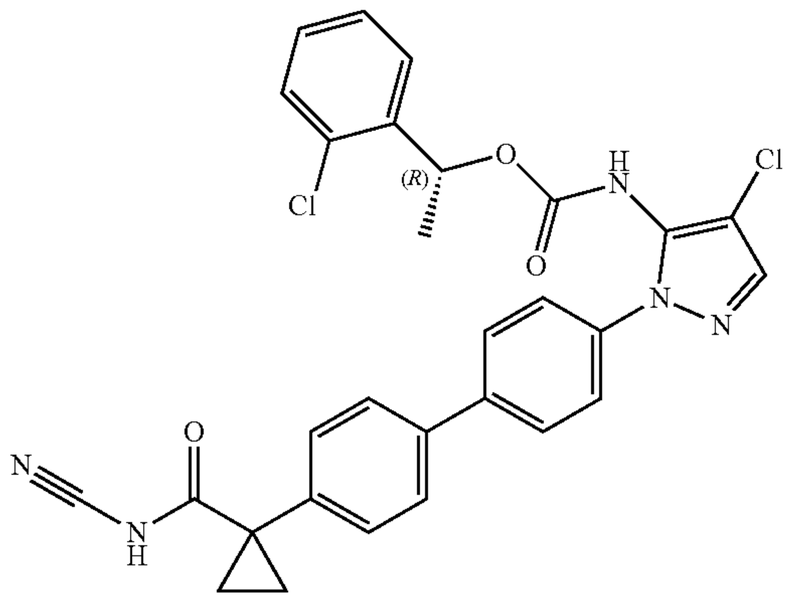


and the CY ring



individually. An exemplary molecule with this structure is Compound 25, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

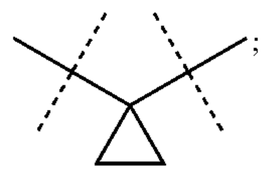
Compound 25



**[0376]** Embodiment 37A. The compound of Embodiment 5A, wherein:

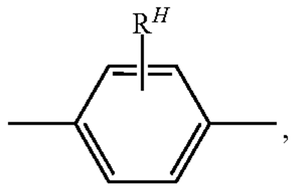
**[0377]** $R^A$ is CONHCN

**[0378]** $L^1$ is



and

**[0379]** in the ring

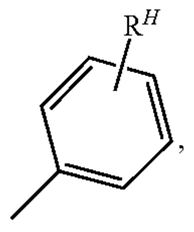


$R^H$ is —F.

**[0380]** Embodiment 38A. The compound of Embodiment 37A, wherein:

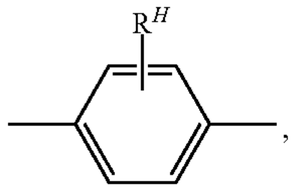
**[0381]** $R^C$ is —F; and

**[0382]** in the CY ring

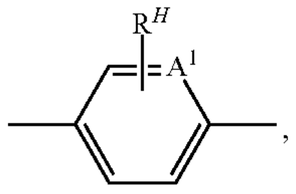


$R^H$ is —Cl.

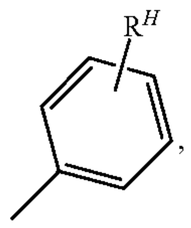
**[0383]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

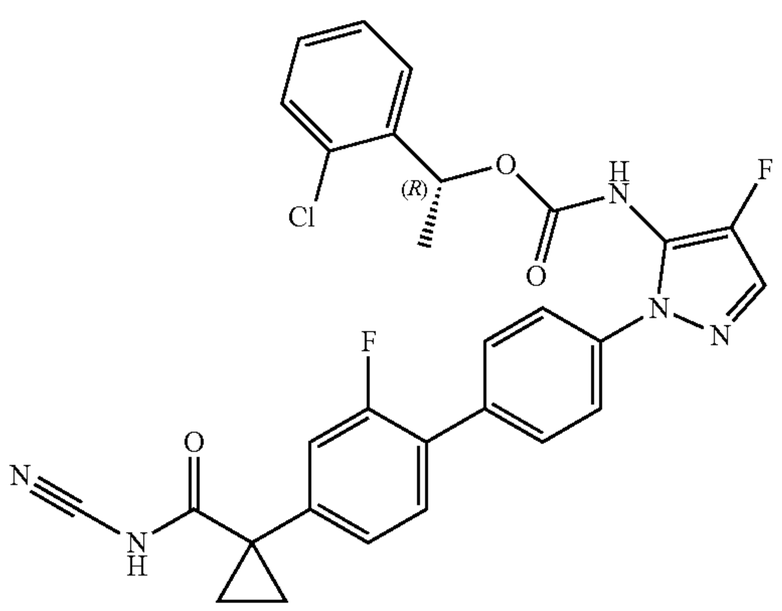


and the CY ring



individually. An exemplary molecule with this structure is Compound 26, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate.

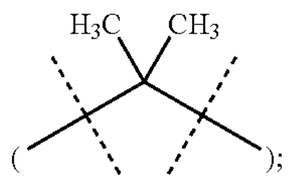
Compound 26



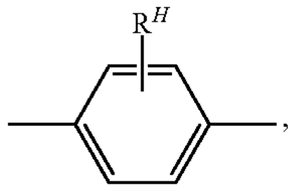
**[0384]** Embodiment 39A. The compound of Embodiment 2A, wherein:

**[0385]** $R^A$ is $CO_2H$;

**[0386]** $L^1$ is dimethylmethane

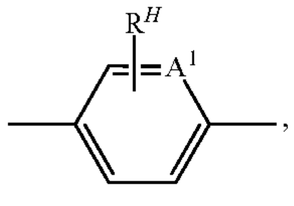


**[0387]** in the ring



$R^H$ is —H;

**[0388]** in the ring

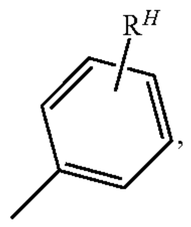


$A^1$ is CH and $R^H$ is —H;

**[0389]** and $R^C$ is —CN.

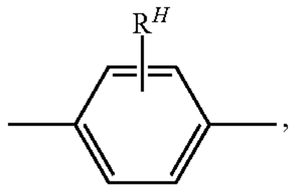
**[0390]** Embodiment 40A. The compound of Embodiment 39A, wherein:

**[0391]** in the CY ring

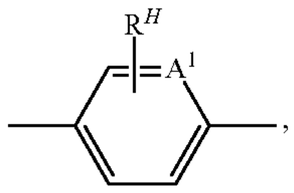


$R^H$ is —Cl.

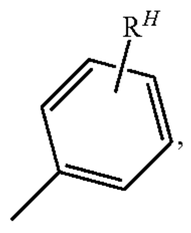
**[0392]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

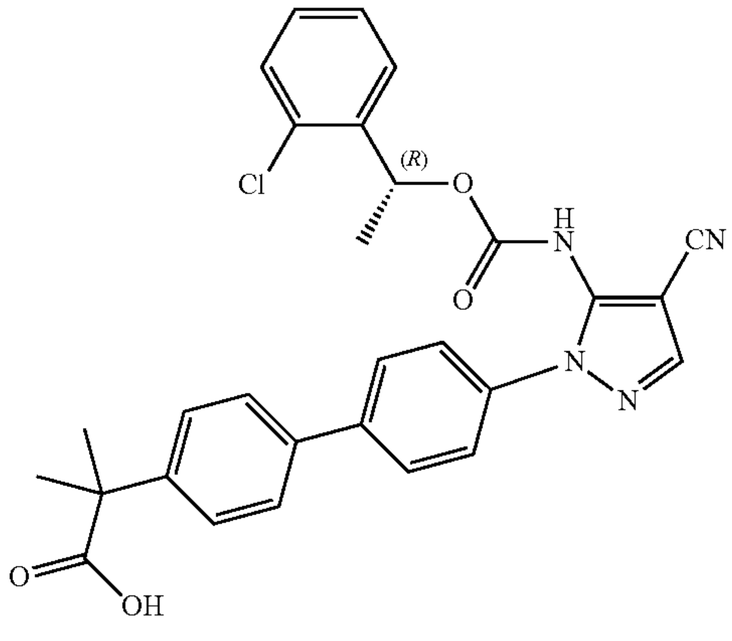


and the CY ring



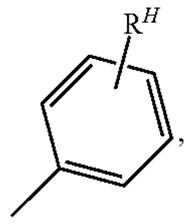
individually. An exemplary molecule with this structure is Compound 27, (R)-2-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid.

Compound 27



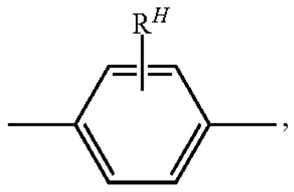
**[0393]** Embodiment 41A. The compound of Embodiment 39A, wherein:

**[0394]** in the CY ring

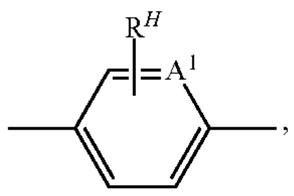


$R^H$ is —H.

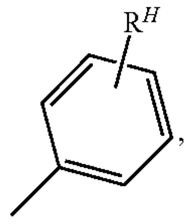
**[0395]** In this embodiment, it is understood that $R^H$ can be located at any available carbon atom in the ring



the ring

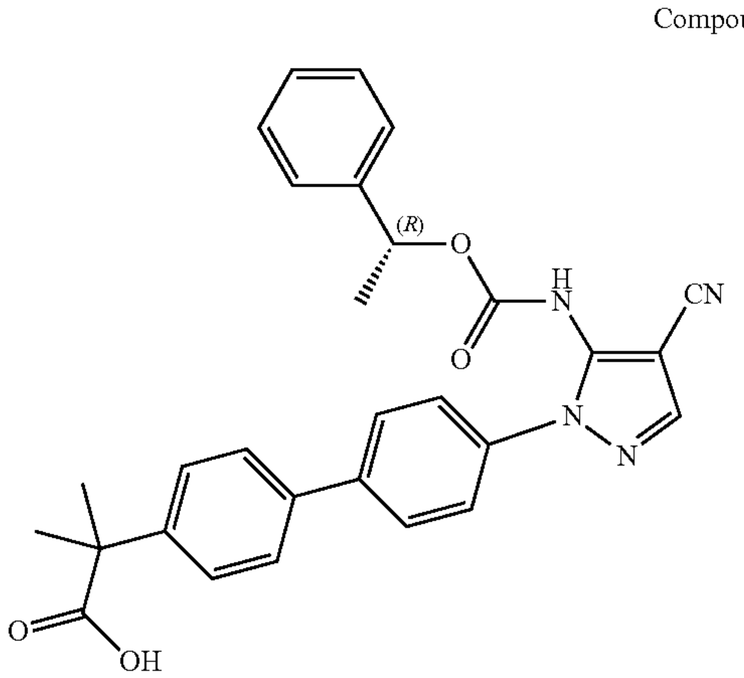


and the CY ring



individually. An exemplary molecule with this structure is Compound 28, (R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid.

Compound 28



**[0396]** Embodiment 42A. The compound of Embodiment 1A, wherein $R^G$ is in an R or S configuration.

**[0397]** Embodiment 43A. The compound of Embodiment 2A wherein the compound is selected from Table 1.

**[0398]** Embodiment 44A. The compound of Embodiment 43A wherein the compound is (R)-1-(4-(5-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(3-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-3-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chloro-4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-2-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid, (R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid.

**[0399]** Embodiment 45A. A compound of any one of Embodiments 1A-44A for preparation of mendicant for treating a LPA-dependent disease or condition.

**[0400]** The compounds of Table 1 are exemplary of the invention but not limiting, wherein additional compounds are prepared according to the appropriately modified procedures of the examples for preparation of compounds 1-28.

TABLE 1

| Compound | Name |
|---|---|
| 1 | (R)-1-(4-(5-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid |
| 2 | (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid |
| 3 | (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 4 | (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 5 | (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 6 | (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 7 | (R)-1-(3-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 8 | (R)-1-(2-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 9 | (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-3-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 10 | (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 11 | (R)-1-(2-chloro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 12 | (R)-1-(2-chloro-4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 13 | (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 14 | (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid |
| 15 | (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate |
| 16 | (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate |
| 17 | (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate |
| 18 | (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate |
| 19 | (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate |
| 20 | (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate |
| 21 | (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate |
| 22 | (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate |
| 23 | (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate |
| 24 | (R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate |
| 25 | (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate |
| 26 | (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate |
| 27 | (R)-2-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid |
| 28 | (R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid |

## EXAMPLES

**[0401]** HPLC Methods

**[0402]** HPLC traces for examples synthesized were recorded using a HPLC consisting of Agilent HPLC pumps, degasser and UV detector, equipped with an Agilent 1100 series auto-sampler. A MS detector (APCI) PE Sciex API 150 EX was incorporated for purposes of recording mass spectral data. HPLC/mass traces were obtained using one of three chromatographic methods:

**[0403]** Method 1: Column Zorbax C18, size 4.6 mm×7.5 cm; Solvent A: 0.05% TFA in water, Solvent B: 0.05% TFA in acetonitrile; Flow rate—0.7 mL/min; Gradient: 5% B to 100% B in 9 min, hold at 100% B for 4 min and 100% B to 5% B in 0.5 min; UV detector—channel 1=220 nm, channel 2=254 nm.

**[0404]** Method 2: Column Zorbax C18, size 4.6 mm×7.5 cm; Solvent A: 0.05% TFA in water, Solvent B: 0.05% TFA in acetonitrile; Flow rate—0.7 mL/min; Gradient: 5% B to

100% B in 5 min, hold at 100% B for 2 min and 100% B to 5% B in 0.5 min; UV detector—channel 1=220 nm, channel 2=254 nm.

**[0405]** Method 3: SunFire™ (Waters) C18, size 2.1 mm×50 mm; Solvent A: 0.05% TFA in water, Solvent B: 0.05% TFA in acetonitrile; Flow rate—0.8 mL/min; Gradient: 10% B to 90% B in 2.4 min, hold at 90% B for 1.25 min and 90% B to 10% B in 0.25 min, hold at 10% B for 1.5 min.; UV detector—channel 1=220 nm, channel 2=254 nm.

**[0406]** Method 4: Column Zorbax C18, size 4.6 mm×50 mm, 5p particle size; Solvent A: acetonitrile; Solvent B: 0.1% HCOOH in water; Flow Rate—1.5 mL/min; Gradient 10-95% A in 2.5 minutes.

### Example 1: (R)-1-(4-(5-(5-(((1-(2-chlorophenyl) ethoxy)carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl) pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid [Compound 1]

#### Step 1: Ethyl 2-(6-chloro-3-pyridyl)-2H-pyrazole-3-carboxylate

**[0407]** A mixture of ethyl pyruvate (3.89 mL, 35.0 mmol), dimethylformamide dimethylacetal (9.30 mL, 70.0 mmol) and para-toluene sulfonic acid (10 mg) was stirred at room temperature overnight and then heated to 80° C. for 2 hours. The mixture was cooled to room temperature and concentrated in vacuo to dryness. The crude ethyl 4-(dimethylamino)-2-oxo-3-butenoate was dissolved in ethanol (90 mL) and treated with (6-chloro-3-pyridyl)hydrazine hydrochloride (7.5 g, 35.0 mmol) and concentrated hydrochloric acid (250 μL). The resulting mixture was heated to 88° C. overnight, then cooled to room temperature and concentrated in vacuo. The crude residue was purified by silica-gel column chromatography, eluting with a hexanes/ethyl acetate gradient. Two regioisomers were separated—the desired isomer A [ethyl 2-(6-chloro-3-pyridyl)-2H-pyrazole-3-carboxylate] eluted off the column first and the undesired regioisomer B [ethyl 1-(6-chloro-3-pyridyl)-1H-pyrazole-3-carboxylate] was isolated as the more polar compound. The desired product was obtained as a yellow oil, which solidified upon standing.

**[0408]** Isomer A, Yield=216 mg (2%). Method 3, Rt 2.68 min. MS (ESI) m/z 251.9 [M+H$^+$]. $^1$H NMR ($CDCl_3$) δ 8.50 (d, J=2.0 Hz, 1H); 7.78 (dd, $J_1$=6.8 Hz, $J_2$=2.0 Hz, 1H); 7.75 (d, J=1.6 Hz, 1H); 7.43 (d, J=6.8 Hz, 1H); 7.08 (d, J=1.6 Hz, 1H); 4.28 (q, J=5.6 Hz, 2H); 1.31, (t, J=5.6 Hz, 3H).

**[0409]** Isomer B, Yield=150 mg (1.7%). Method 3, Rt 2.70 min. MS (ESI) m/z 251.9 [M+H$^+$]. $^1$H NMR ($CDCl_3$) δ 8.77 (d, J=2.4 Hz, 1H); 8.15 (dd, $J_1$=7.2 Hz, $J_2$=2.4 Hz, 1H); 7.96 (d, J=2.0 Hz, 1H); 7.46 (d, J=6.8 Hz, 1H); 7.04 (d, J=2.0 Hz, 1H); 4.45 (q, J=5.6 Hz, 2H); 1.43, (t, J=5.6 Hz, 3H).

#### Step 2: 2-(6-Chloro-3-pyridyl)-2H-pyrazole-3-carboxylic acid

**[0410]** A solution of ethyl 2-(6-chloro-3-pyridyl)-2H-pyrazole-3-carboxylate [Example 1, Step 1] (205 mg, 0.814 mmol) in THF (4 mL) was treated with a 2 M aqueous LiOH solution (4 mL) and the resulting mixture was stirred vigorously at room temperature for 16 hours. LCMS showed completed conversion to product. The reaction mixture was transferred to a separatory funnel and treated with 0.1 N HCl aqueous solution to bring the pH to approximately 1. The product was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to yield the product as a white solid. Yield=190 mg (quantitative). Method 3, Rt 1.71 min (broad). MS (ESI) m/z 224.5 [M+H$^+$].

#### Step 3: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-(6-chloro-3-pyridyl)-2H-pyrazole

**[0411]** 2-(6-Chloro-3-pyridyl)-2H-pyrazole-3-carboxylic acid [Example 1, Step 2] (190 mg, 0.82 mmol) was suspended in dichloromethane (4 mL) and treated with a catalytic amount of N,N-dimethylformamide (2 drops) at room temperature. The reaction mixture was cooled to 0° C. with an ice/water bath. Oxalyl chloride (143 μL, 1.64 mmol) was added dropwise and the resulting mixture was stirred at 0° C. for 15 minutes and at room temperature for 2 hours. An aliquot was dissolved in methanol and subjected to LCMS analysis, which indicated complete conversion to the corresponding acid chloride. The volatiles were removed under reduced pressure to yield the crude acid chloride as a white solid. This material was suspended in ethyl acetate (4 mL) and treated with a solution of $NaN_3$ (107 mg, 1.64 mmol) in water (4 mL) under vigorous magnetic stirring at room temperature. After 1 hour, an aliquot was dissolved in methanol and subjected to LCMS analysis, which indicated complete conversion to the corresponding acyl azide. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum at room temperature to yield the crude acyl azide as a white solid. This material was suspended in toluene (4 mL) and heated to 95° C. with stirring for 30 minutes, when gas evolution was observed. (R)-1-(o-Chlorophenyl)-1-ethanol (157 mg, 1.0 mmol) was added and the resulting mixture was heated to 65° C. overnight. The reaction mixture was cooled to room temperature, concentrated in vacuo to dryness and the crude residue was directly purified by silica-gel chromatography, eluting with a hexanes/ethyl acetate gradient. The pure product was obtained as a colorless oil. Yield=308 mg (quantitative). Method 3, Rt 2.97 min. MS (ESI) m/z 377.2 [M+H$^+$].

#### Step 4: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-(6-chloro-3-pyridyl)-4-fluoro-2H-pyrazole

**[0412]** Selectfluor® (236 mg, 0.67 mmol) was added to a stirring solution containing 3-[(R)-1-(o-chlorophenyl) ethoxycarbonylamino]-2-(6-chloro-3-pyridyl)-2H-pyrazole [Example 1, Step 3] (100 mg, 0.27 mmol) in acetonitrile (2.7 mL) and glacial acetic acid (270 μL) at room temperature. The resulting mixture was stirred overnight and then the volatiles were removed in vacuo. The residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$ aqueous and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and evaporated. Purification by preparative thin layer chromatography (TLC) eluting with a 4:1 v/v mixture of hexanes/ethyl acetate furnished the pure product as a colorless film. Yield=42 mg (40%). Method 3, Rt 3.04 min. MS (ESI) m/z 395.3 [M+H$^+$].

#### Step 5: (R)-1-(4-(5-(5-(((1-(2-chlorophenyl)ethoxy) carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid

**[0413]** A stirring mixture of 3-[(R)-1-(o-chlorophenyl) ethoxycarbonylamino]-2-(6-chloro-3-pyridyl)-4-fluoro-2H-

pyrazole [Example 1, Step 4] (42 mg, 0.107 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (360 μL) and 4-[(1-methoxycarbonyl)cyclopropyl] phenylboronic acid pinacol ester (48 mg, 0.161 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.005 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the crude product was directly dissolved in THF (1 mL) and treated with a 1 M LiOH aqueous solution (1 mL). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the residue was purified by preparative thin layer chromatography on silica-gel, eluting with a 50:50 v/v hexanes/ethyl acetate mixture. Yield=19 mg (34%). Method 3, Rt 2.98 min. MS (ESI) m/z 521.5 [$M+H^+$].

Example 2: (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl) pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid [Compound 2]

Step 1: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-4-chloro-2-(6-chloro-3-pyridyl)-2H-pyrazole

**[0414]** A solution of 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(6-chloro-3-pyridyl)-2H-pyrazole [Example 1, Step 3] (158 mg, 0.42 mmol) in acetonitrile (2.1 mL) was treated with N-chlorosuccinimide (64 mg, 0.48 mmol) under stirring at room temperature. The resulting mixture was heated to 80° C. for 1 hour. The resulting mixture was cooled to room temperature and directly purified by preparative thin layer chromatography, eluting with a 4:1 v/v mixture of hexanes/ethyl acetate, respectively. The desired product was isolated with Rf=0.2 as a white solid. Yield=13 mg (8%). Method 3, Rt 3.09 min. MS (ESI) m/z 411.4 [$M+H^+$].

Step 2: (R)-1-(4-(5-(4-chloro-5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)cyclopropane-1-carboxylic acid

**[0415]** A stirring mixture of 3-[(R)-1-(o-Chlorophenyl) ethoxycarbonylamino]-4-chloro-2-(6-chloro-3-pyridyl)-2H-pyrazole [Example 2, Step 1] (13 mg, 0.032 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (300 μL) and methyl 1-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxylate (15 mg, 0.048 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (4 mg, 0.0032 mmol). The resulting mixture was heated to 85° C. and stirred for 8 hours at that temperature. The reaction mixture was cooled to room temperature and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the crude product was directly dissolved in THF (1 mL) and treated with a 1 M LiOH aqueous solution (1 mL). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the residue was purified by preparative thin layer chromatography on silica-gel, eluting with a 50:50 v/v hexanes/ethyl acetate mixture. Yield=1.7 mg (10%). Method 3, Rt 3.07 min. MS (ESI) m/z 537.1 [$M+H^+$].

Example 3: (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy) carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid. [Compound 3]

Step 1: Ethyl-2-acetyl-3-(dimethylamino)acrylate

**[0416]** A mixture of ethyl acetoacetate (200.0 g, 1.54 mol) and dimethylformamide dimethyl acetal (219.7 g, 1.84 mol) was stirred at room temperature for 16 hours. Reaction was monitored by thin layer chromatography (30% ethyl acetate in hexanes). The reaction mixture was concentrated under reduced pressure to yield 290.0 g of crude product, which was taken to the next step without further purification. Method 4, Rt 1.584 min. MS (ESI) m/z 186.00-187.00 [$M+H^+$].

**[0417]** $^1H$ NMR (DMSO-$d_6$) δ 7.60 (s, 1H); 4.13 (q, 2H); 3.34-2.90 (br, 6H); 2.14 (s, 3H); 1.24 (t, 3H).

Step 2: Ethyl 1-(p-bromophenyl)-5-methyl-1H-pyrazole-4-carboxylate

**[0418]** To a solution of ethyl-2-acetyl-3-(dimethylamino) acrylate [Example 3, Step 1](290.0 g, 1.57 mol) in ethanol (4.35 L) was added 4-bromophenyl hydrazine hydrochloride (315.0 g, 1.41 mol) at room temperature. The resulting mixture was refluxed for 3 hours. Reaction progress was monitored by thin layer chromatography (40% ethyl acetate in hexanes). The reaction mixture was concentrated to dryness under reduced pressure to yield the crude product, which was recrystallized with 10% of diethyl ether in hexane to yield 174.0 g of the title compound as a pale yellow solid. The mother liquor was concentrated to dryness and recrystallized with 10% of diethyl ether in hexane to yield another 116.0 g of product. Total yield=290.0 g (60%). Method 4, Rt 2.954 min. MS (ESI) m/z 309.00-310.00 [$M+H^+$].

**[0419]** $^1H$ NMR (DMSO-$d_6$) δ 8.03 (s, 1H); 7.78 (d, 2H); 7.53 (d, 2H); 4.26 (m, 2H); 3.34 (s, 3H); 1.30 (m, 3H).

Step 3: 1-(p-Bromophenyl)-5-methyl-1H-pyrazole-4-carboxylic acid

**[0420]** To a solution of ethyl 1-(p-bromophenyl)-5-methyl-1H-pyrazole-4-carboxylate [Example 3, Step 2] (200.0 g, 0.65 mol) in ethanol (1.4 L) and was added an aqueous solution of KOH (72.45 g, 1.29 mol) dissolved in water (1 L) at room temperature. The resulting mixture was refluxed for 3 hours. Reaction was monitored by thin layer chromatography (10% methanol in chloroform). The reaction mixture was concentrated under reduced pressure to yield the corresponding potassium salt, which was dissolved in water and washed with diethyl ether. The aqueous layer was neutralized with aqueous 6N HCl solution and extracted with ethyl acetate. The organic layer was washed with water, brine then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield 172.0 g of

product as an off white solid (Yield=95%). Method 4, Rt 2.341 min. MS (ESI) m/z 280.8-280.9 [M+H$^+$].

**[0421]** $^1$H NMR (DMSO-d$_6$) δ 12.48 (s, 1H); 7.99 (s, 1H); 7.77 (d, 2H); 7.53 (d, 2H); 3.36 (s, 3H).

Step 4: 1-(p-Bromophenyl)-5-methyl-1H-pyrazole

**[0422]** 1-(p-Bromophenyl)-5-methyl-1H-pyrazole-4-carboxylic acid [Example 3, Step 3](300.0 g, 1.07 mol) was placed in a 3 liter round bottom flask and was stirred at 260° C. (bath temp 280 to 300° C.) for 10 h. Reaction was monitored by thin layer chromatography (10% methanol in chloroform). The reaction mixture was diluted with diethyl ether and washed with 10% of sodium carbonate, water, and brine then dried over sodium sulfate and filtered. The organic layer was concentrated under reduced pressure to yield 200.0 g of product, as a pale brown liquid (Yield-79%). Method 4, Rt 2.739 min. MS (ESI) m/z 237.0-239.9 [M+H$^+$].

Step 5:
2-(p-Bromophenyl)-2H-pyrazole-3-carboxylic acid

**[0423]** A solution of 1-(p-bromophenyl)-5-methyl-1H-pyrazole [Example 3, Step 4](200.0 g, 0.84 mol) in tert-butanol (2 L) was treated with an aqueous solution of KOH (141.7 g, 2.53 mol) dissolved in water (1 L) at RT followed by $KMnO_4$ (266.6 g, 1.69 mol). The resulting mixture was refluxed for 3 hours then the same amount of $KMnO_4$ was added twice within a 1-hour interval, continuing heating for 10 hours. Reaction was monitored by thin layer chromatography (10% methanol in chloroform). The reaction mixture was filtered through a pad of Celite and washed with hot water. The aqueous solution washed with diethyl ether, then neutralized with 6N HCl solution and extracted with ethyl acetate. The organic layer was washed with water, brine then dried over sodium sulfate, filtered and concentrated under reduced pressure to yield 120.0 g of product, as a pale yellow solid (Yield=53%). Method 4, Rt 2.210 min. MS (ESI) m/z 269.00 [M+H$^+$].

**[0424]** $^1$H NMR (DMSO-d$_6$) δ 13.40 (s, 1H); 7.79 (s, 1H); 7.66 (d, 2H); 7.43 (d, 2H); 7.03 (s, 1H).

Step 6: 3-[(R)-1-Phenylethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole

**[0425]** A suspension of 2-(p-bromophenyl)-2H-pyrazole-3-carboxylic acid [Example 3, Step 5] (1.69 g, 6.36 mmol) in toluene (64 mL) was treated with triethylamine (1.07 mL, 7.63 mmol), (R)-1-phenyl-1-ethanol (1.16 g, 9.54 mmol) and diphenylphosphoryl azide (1.94 g, 7.04 mmol) sequentially. The resulting solution was heated to 90° C. for 6 hours with reaction monitoring by LCMS. The reaction was cooled to room temperature and the volatiles removed in vacuo. The crude residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate gradient. The product was obtained as a yellow oil, which solidified upon standing. Yield=839 mg (34%). Method 3, Rt 3.05 min. MS (ESI) m/z 388.0 [M+H$^+$].

Step 7: 3-[(R)-1-Phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole

**[0426]** A stirred solution of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole [Example 3, Step 6] (385 mg, 1.0 mmol) in acetonitrile (3.3 mL) and acetic acid (1.3 mL) was treated with Selectfluor® (354 mg, 1.0 mmol) and the resulting mixture was stirred at room temperature overnight. LCMS indicates 90% conversion to product. Another portion of Selectfluor® (70 mg) was added and the reaction was allowed to stir at room temperature for another 10 hours. LCMS shows reaction complete. The reaction mixture was concentrated in vacuo and the crude residue was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated $NaHCO_3$ aqueous and brine. Organics were dried over anhydrous $MgSO_4$, filtered and evaporated. The thick amber film was purified by silica-gel chromatography, eluting with a hexanes/ethyl acetate gradient. Yield=278 mg (69%). Method 3, Rt 3.36 min. MS (ESI) m/z 404-.1-406.0 [M+H$^+$].

Step 8: (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid

**[0427]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 3, Step 7] (55 mg, 0.136 mmol), 2:1 v/v mixture of toluene and ethanol (1.4 mL), 2M $Na_2CO_3$ aqueous solution (450 μL) and 4-[(1-methoxycarbonyl)cyclopropyl]phenylboronic acid pinacol ester (54 mg, 0.180 mmol) was degassed under $N_2$ for 10 minutes and treated with Pd[Ph$_3$P]$_4$ (8 mg, 0.0068 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the crude product was directly dissolved in THF (1 mL) and treated with a 1 M LiOH aqueous solution (1 mL). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the residue was purified by preparative thin layer chromatography on silica-gel, eluting with a 95:5 v/v dichloromethane/methanol mixture. Yield=28 mg (43%). Method 3, Rt 3.25 min. MS (ESI) m/z 486.2 [M+H$^+$].

Example 4: (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 4]

Step 1: 3-[(R)-1-Phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole

**[0428]** N-Chlorosuccinimide (97 mg, 0.73 mmol) was added to a stirring solution containing 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole [Example 3, Step 6] (281 mg, 0.73 mmol) in acetonitrile (3.7 mL) at room temperature. The resulting mixture was heated to 80° C. for 5 hours, after which time the reaction was deemed complete by LCMS. The reaction mixture was cooled to room temperature, concentrated in vacuo and purified directly via silica-gel column chromatography, eluting with a hexanes/ethyl acetate gradient. The product was obtained as a yellow oil, which solidified upon standing. Yield=277 mg (91%). Method 3, Rt 3.24 min. MS (ESI) m/z 422.1 [M+H$^+$].

Step 2: Methyl 1-(4'-{5-[(R)-1-phenylethoxycarbonylamino]-4-chloro-1H-pyrazol-1-yl}-4-biphenylyl) cyclopropanecarboxylate

**[0429]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 4, Step 1] (43 mg, 0.103 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (343 μL) and methyl 1-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxylate (40 mg, 0.134 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.052 mmol). The resulting mixture was heated to 85° C. and stirred overnight at that temperature. The reaction mixture was cooled to room temperature and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the residue was purified by silica-gel chromatography, eluting with a hexanes/ethyl acetate gradient. Yield=45 mg (85%). Method 3, Rt 3.34 min. MS (ESI) m/z 516.1 $[M+H^+]$.

Step 3: (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy) carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid

**[0430]** Methyl 1-(4'-{5-[(R)-1-phenylethoxycarbonylamino]-4-chloro-1H-pyrazol-1-yl}-4-biphenylyl)cyclopropanecarboxylate [Example 4, Step 2] (45 mg, 0.087 mmol) was dissolved in THF (1 mL) and treated with a 1 M LiOH aqueous solution (1 mL). The resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the residue was purified by preparative thin layer chromatography on silica-gel, eluting with a 95:5 v/v dichloromethane/methanol mixture. Yield=23 mg (53%). Method 3, Rt 3.11 min. MS (ESI) m/z 502.3 $[M+H^+]$.

Example 5: (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy) carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 5]

Step 1: 3-[(R)-1-Phenylethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole-4-carbonitrile

**[0431]** A stirring suspension containing 5-amino-1-(4-bromophenyl)-1H-pyrazole-4-carbonitrile (262 mg, 1.0 mmol) and triphosgene (436 mg, 1.5 mmol) in THF (4.8 mL) was treated with a solution of triethylamine (730 μL, 5.26 mmol) in toluene (40 mL) dropwise. The resulting mixture was heated to 90° C. for 30 minutes and then treated with (R)-1-phenylethanol (160 μL, 1.3 mmol). The reaction was heated to 105° C. for 3 hours, after which time monitoring by TLC (5% acetone in toluene) indicated one main product formed. The reaction was cooled to room temperature and concentrated in vacuo. The residue was directly purified by preparative thin layer chromatography, eluting with a 95:5 v/v mixture of toluene and acetone, respectively. The product was obtained as a solid. Yield=153 mg (37%). Method 3, Rt 3.53 min. MS (ESI) m/z 411.5-413.6 $[M+H^+]$.

Step 2: Methyl 1-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxylate

**[0432]** 1-(p-Bromophenyl)cyclopropanecarboxylic acid (1.22 g, 5.0 mmol) was dissolved in methanol (20 mL), cooled to −20° C. using ice water (2 parts) and salt (1 part). To this solution, thionyl chloride (1.45 mL, 20.0 mmol) was added dropwise. After completion of addition, the reaction was stirred for 15 minutes at −20° C. and then allowed to warm to room temperature over a period of 2 hours. LCMS indicated product formation. The reaction was concentrated in vacuo and the residue was partitioned between dichloromethane and an aqueous saturated $Na_2CO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to yield methyl 1-(p-bromophenyl)cyclopropanecarboxylate (1.08 g, 4.2 mmol, 84%). This material was dissolved in 1,4-dioxane (20 mL), treated with bis(pinacolato)diboron (3.19 g, 12.1 mmol), KOAc (1.24 g, 12.6 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (328 mg, 0.54 mmol). The resulting mixture was heated to 100° C. overnight and then cooled to room temperature, filter through a pad of CELITE and rinsed with methanol. The filtrate was concentrated in vacuo. Part of the crude material was purified by preparative thin layer chromatography on silica gel, eluting with hexanes. The product is a white solid. Yield=270 mg. Method 3, Rt 3.08 min. MS (ESI) m/z 303.4 $[M+H^+]$.

Step 3: Methyl 1-(4'-{5-[(R)-1-phenylethoxycarbonylamino]-4-cyano-1H-pyrazol-1-yl}-4-biphenylyl) cyclopropanecarboxylate

**[0433]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole-4-carbonitrile [Example 5, Step 1] (58 mg, 0.14 mmol), 1,4-dioxane (2 mL), 2M $Na_2CO_3$ aqueous solution (315 μL) and methyl 1-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] cyclopropanecarboxylate [Example 5, Step 2] (51 mg, 0.17 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (23 mg, 0.02 mmol). The resulting mixture was heated to 95° C. overnight. The reaction mixture was cooled to room temperature, filtered through a pad of CELITE and rinsed with methanol. The filtrates were concentrated in vacuo and the crude residue was purified directly by preparative thin layer chromatography, eluting with 70:30 v/v mixture of hexanes and ethyl acetate, respectively. Yield=18 mg (26%). Method 3, Rt 3.13 min. MS (ESI) m/z 507.6 $[M+H^+]$.

Step 4: (R)-1-(4'-(4-cyano-5-(((1-phenylethoxy) carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid

**[0434]** Methyl 1-(4'-{5-[(R)-1-phenylethoxycarbonylamino]-4-cyano-1H-pyrazol-1-yl}-4-biphenylyl)cyclopropanecarboxylate [Example 5, Step 3] (18 mg, 0.03 mmol) was dissolved in THF (1 mL) and treated with a 1 M LiOH aqueous solution (1 mL) and the resulting mixture was stirred at room temperature overnight. Reaction progress was monitored by thin layer chromatography (30% ethyl acetate in hexanes). The reaction was treated with 1 M aqueous HCl solution (3 mL) and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude residue was purified by preparative thin layer chromatography, eluting with a 70:30 v/v mixture of toluene and acetone, respectively. The product was obtained as a white solid. Yield=10 mg (71%). Method 3, Rt 2.77 min. MS (ESI) m/z 493.6 $[M+H^+]$.

Example 6: (R)-1-(4'-(5-(((1-(2-chlorophenyl) ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 6]

Step 1: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole-4-carbonitrile

**[0435]** A stirring suspension containing 5-amino-1-(4-bromophenyl)-1H-pyrazole-4-carbonitrile (262 mg, 1.0 mmol) and triphosgene (436 mg, 1.5 mmol) in THF (4.8 mL) was treated with a solution of triethylamine (730 μL, 5.26 mmol) in toluene (40 mL) dropwise. The resulting mixture was heated to 90° C. for 30 minutes and then treated with (R)-1-(2-chlorophenyl)ethanol (172 μL, 1.3 mmol). The reaction was heated to 105° C. for 3 hours, after which time monitoring by TLC (5% acetone in toluene) indicated one main product formed. The reaction was cooled to room temperature and concentrated in vacuo. The residue was directly purified by preparative thin layer chromatography, eluting with a 95:5 v/v mixture of toluene and acetone, respectively. The product was obtained as a solid. Yield=153 mg (37%). Method 3, Rt 2.94 min. MS (ESI) m/z 445.5-447.5 [M+H$^+$].

Step 2: Methyl 1-(4'-{5-[(R)-1-(o-chlorophenyl) ethoxycarbonylamino]-4-cyano-1H-pyrazol-1-yl}-4-biphenylyl)cyclopropanecarboxylate

**[0436]** A stirring mixture of 3-[(R)-1-(o-chlorophenyl) ethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole-4-carbonitrile [Example 6, Step 1] (51 mg, 0.14 mmol), 1,4-dioxane (2 mL), 2M $Na_2CO_3$ aqueous solution (315 μL) and methyl 1-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxylate [Example 5, Step 2] (51 mg, 0.17 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (23 mg, 0.02 mmol). The resulting mixture was heated to 95° C. overnight. The reaction mixture was cooled to room temperature, filtered through a pad of CELITE and rinsed with methanol. The filtrates were concentrated in vacuo and the crude residue was purified directly by preparative thin layer chromatography, eluting with 70:30 v/v mixture of hexanes and ethyl acetate, respectively. Yield=25 mg (33%). Method 3, Rt 3.20 min. MS (ESI) m/z 541.3 [M+H$^+$].

Step 3: (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy) carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid

**[0437]** Methyl 1-(4'-{5-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-4-cyano-1H-pyrazol-1-yl}-4-biphenylyl) cyclopropanecarboxylate [Example 6, Step 2] (25 mg, 0.03 mmol) was dissolved in THF (1 mL) and treated with a 1 M LiOH aqueous solution (1 mL) and the resulting mixture was stirred at room temperature overnight. Reaction progress was monitored by thin layer chromatography (30% ethyl acetate in hexanes). The reaction was treated with 1 M aqueous HCl solution (3 mL) and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude residue was purified by preparative thin layer chromatography, eluting with a 70:30 v/v mixture of toluene and acetone, respectively. The product was obtained as a white solid. Yield=12 mg (76%). Method 3, Rt 2.88 min. MS (ESI) m/z 527.5 [M+H$^+$].

Example 7: (R)-1-(3-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 7]

**[0438]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 3, Step 7] (55 mg, 0.136 mmol), 2:1 v/v mixture of toluene and ethanol (1.4 mL), 2M $Na_2CO_3$ aqueous solution (450 μL) and 4-(1-carboxycyclopropyl)-3-fluorophenylboronic acid pinacol ester (55 mg, 0.180 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (8 mg, 0.0068 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature and treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the crude product was purified by preparative thin layer chromatography on silica-gel, eluting with a 95:5 v/v dichloromethane/methanol mixture. Yield=7 mg (10%). Method 3, Rt 3.26 min. MS (ESI) m/z 504.2 [M+H$^+$].

Example 8—(R)-1-(2-fluoro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 8]

**[0439]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 3, Step 7] (55 mg, 0.136 mmol), 2:1 v/v mixture of toluene and ethanol (1.4 mL), 2M $Na_2CO_3$ aqueous solution (450 μL) and 4-(1-carboxycyclopropyl)-2-fluorophenylboronic acid pinacol ester (55 mg, 0.180 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (8 mg, 0.0068 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature and treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the crude product was purified by preparative thin layer chromatography on silica-gel, eluting with a 95:5 v/v dichloromethane/methanol mixture. Yield=19 mg (28%). Method 3, Rt 3.27 min. MS (ESI) m/z 504.2 [M+H$^+$].

Example 9: (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy) carbonyl)amino)-1H-pyrazol-1-yl)-3-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 9]

**[0440]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 4, Step 1] (43 mg, 0.103 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (343 μL) and 1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxylic acid (41 mg, 0.134 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.052 mmol). The resulting mixture was heated to 85° C. and stirred overnight at that

temperature. The reaction mixture was cooled to room temperature, treated carefully with 1 M HCl aqueous to bring the solution pH ~1. Ethyl acetate (1 mL) was added and the resulting mixture stirred vigorously for 5 minutes. The organic layer was separated and purified directly by preparative thin layer chromatography, eluting with 95:5 v/v mixture of dichloromethane and methanol, respectively. Yield=17 mg (32%). Method 3, Rt 3.33 min. MS (ESI) m/z 520.2 [M+H$^+$].

Example 10: (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 10]

**[0441]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 4, Step 1] (43 mg, 0.103 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (343 μL) and 1-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxylic acid (41 mg, 0.134 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.052 mmol). The resulting mixture was heated to 85° C. and stirred overnight at that temperature. The reaction mixture was cooled to room temperature, treated carefully with 1 M HCl aqueous to bring the solution pH ~1. Ethyl acetate (1 mL) was added and the resulting mixture stirred vigorously for 5 minutes. The organic layer was separated and purified directly by preparative thin layer chromatography, eluting with 95:5 v/v mixture of dichloromethane and methanol, respectively. Yield=9 mg (17%). Method 3, Rt 3.14 min. MS (ESI) m/z 520.3 [M+H$^+$].

Example 11: (R)-1-(2-chloro-4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 11]

**[0442]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 3, Step 7] (55 mg, 0.136 mmol), 2:1 v/v mixture of toluene and ethanol (1.4 mL), 2M $Na_2CO_3$ aqueous solution (450 μL) and 1-[3-chloro-4-(dihydroxyboranyl)phenyl]cyclopropane-1-carboxylic acid (43 mg, 0.180 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (8 mg, 0.0068 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature and treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the crude product was purified by preparative thin layer chromatography on silica-gel, eluting with a 95:5 v/v dichloromethane/methanol mixture. Yield=13 mg (19%). Method 3, Rt 3.31 min. MS (ESI) m/z 520.3 [M+H$^+$].

Example 12: (R)-1-(2-chloro-4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 12]

**[0443]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 4, Step 1] (43 mg, 0.103 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (343 μL) and 1-[3-chloro-4-(dihydroxyboranyl)phenyl]cyclopropane-1-carboxylic acid (32 mg, 0.134 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.052 mmol). The resulting mixture was heated to 85° C. and stirred overnight at that temperature. The reaction mixture was cooled to room temperature, treated carefully with 1 M HCl aqueous to bring the solution pH ~1. Ethyl acetate (1 mL) was added and the resulting mixture stirred vigorously for 5 minutes. The organic layer was separated and purified directly by preparative thin layer chromatography, eluting with 95:5 v/v mixture of dichloromethane and methanol, respectively. Yield=21 mg (38%). Method 3, Rt 3.20 min. MS (ESI) m/z 536.1 [M+H$^+$].

Example 13: (R)-1-(4'-(4-fluoro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 13]

**[0444]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 3, Step 7] (55 mg, 0.136 mmol), 2:1 v/v mixture of toluene and ethanol (1.4 mL), 2M $Na_2CO_3$ aqueous solution (450 μL) and 1-[4-(dihydroxyboranyl)-3-methylphenyl]cyclopropane-1-carboxylic acid (30 mg, 0.180 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (8 mg, 0.0068 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature and treated with 1 M HCl aqueous in order to bring pH to 1. The product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. After concentration in vacuo, the crude product was purified by preparative thin layer chromatography on silica-gel, eluting with a 95:5 v/v dichloromethane/methanol mixture. Yield=12 mg (18%). Method 3, Rt 3.13 min. MS (ESI) m/z 500.4 [M+H$^+$].

Example 14: (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-2-methyl-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Compound 14]

**[0445]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 4, Step 1] (43 mg, 0.103 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (343 μL) and 1-[4-(dihydroxyboranyl)-3-methylphenyl]cyclopropane-1-carboxylic acid (29 mg, 0.134 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.052 mmol). The resulting mixture was heated to 85° C. and stirred overnight at that temperature. The reaction mixture was cooled to room temperature, treated carefully with 1 M HCl aqueous to bring the solution pH ~1. Ethyl acetate (1 mL) was added and the resulting mixture stirred vigorously for 5 minutes. The organic layer was separated and purified directly by preparative thin layer chromatography, eluting with 95:5 v/v mixture of dichloromethane and methanol, respectively. Yield=23 mg (43%). Method 3, Rt 3.18 min. MS (ESI) m/z 516.3 [M+H$^+$].

Example 15: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate [Compound 15]

Step 1: 1-(p-Bromophenyl)cyclopropanecarboxamide

**[0446]** A stirring solution of 1-(p-bromophenyl)cyclopropanecarbonitrile (500 mg, 2.25 mmol) in ethanol (5 mL) was treated with a 1 M KOH aqueous solution (0.3 mL) and 30% $H_2O_2$ (3 mL). The resulting mixture was heated to 85° C. for 2 hours. The reaction was cooled to room temperature, quenched with water and the product was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was obtained as a white solid, which was used directly in the next step without any further purification. Yield=0.44 g (81%).

Step 2: 1-[p-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxamide

**[0447]** 1-(p-Bromophenyl)cyclopropanecarboxamide [Example 15, Step 1] (430 mg, 1.8 mmol) was dissolved in 1,4-dioxane (5 mL) and treated with KOAc (210 mg, 2.1 mmol) and bis(pinacolato)diboron (545 mg, 2.1 mmol). The resulting mixture was degassed under $N_2$ for 5 minutes, treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane adduct (73 mg, 0.08 mmol) and heated to 95° C. for 4 hours. The reaction was cooled, filtered through a pad of CELITE and rinsed with ethyl acetate. The filtrates were washed with water and brine. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated. The crude was obtained as a dark oil (0.99 g). This material was used in the next step without further purification.

Step 3: Ethyl (E)-4-(dimethylamino)-2-oxo-but-3-enoate

**[0448]** Ethyl pyruvate (5 g, 43.1 mmol) was dissolved in $CH_2Cl_2$ (86 mL) and treated with dimethylformamide dimethylacetal (5.73 mL, 43.1 mmol). The reaction was stirred at room temperature for 2 hours and concentrated in vacuo. The crude was used as is in the next step. Yield=7.4 g.

Step 4: Ethyl 2-(4-bromophenyl)pyrazole-3-carboxylate

**[0449]** 4-Bromophenyl hydrazine hydrochloride (2.0 g, 8.95 mmol) was dissolved in MeOH (18 mL) and treated with crude ethyl (E)-4-(dimethylamino)-2-oxo-but-3-enoate [Example 15, Step 3] (1.54 g, 9.0 mmol). The resulting mixture was stirred at room temperature for 6 hours. The volatiles were removed in vacuo and the residue was purified by chromatography on silica-gel, eluting with a 95:5 mixture of hexanes/ethyl acetate v/v, increasing the polarity to 9:1 over time. Two isomeric products were isolated: ethyl 2-(4-bromophenyl)pyrazole-3-carboxylate as an orange solid (0.82 g, 2.78 mmol, 31%) and ethyl 1-(4-bromophenyl) pyrazole-3-carboxylate as a red solid (0.44 g, 1.49 mmol, 17%).

**[0450]** Ethyl 2-(4-bromophenyl)pyrazole-3-carboxylate: HPLC (254 nm): Method 2 Rt 5.22 min. MS (ESI) m/z 297 [M+H$^+$]; 294.8 [M+H$^+$]; 252 [(M−EtO)+H$^+$]; 250 [(M−EtO)+H$^+$].

**[0451]** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J=1.9 Hz, 1H); 7.58 (d, J=8.7 Hz, 2H); 7.32 (d, J=8.7 Hz, 2H); 7.03 (d, J=1.9 Hz, 1H); 4.26 (q, J=7.1 Hz, 2H); 1.28 (t, J=7.1 Hz, 3H).

**[0452]** Ethyl 1-(4-bromophenyl)pyrazole-3-carboxylate: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J=2.4 Hz, 1H); 7.65 (d, J=7.2 Hz, 2H); 7.60 (d, J=7.2 Hz, 2H); 7.00 (d, J=2.4 Hz, 1H); 4.44 (q, J=7.0 Hz, 2H); 1.43 (t, J=7.0 Hz, 3H).

Step 5: 2-(4-Bromo-phenyl)-4-fluoro-2H-pyrazole-3-carboxylic acid ethyl ester

**[0453]** Ethyl 2-(4-bromophenyl)pyrazole-3-carboxylate [Example 15, Step 4] (1.08 g, 3.68 mmol) was dissolved in acetonitrile (12 mL) and the resulting mixture was treated with glacial acetic acid (4.6 mL). To this solution, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®, 3.91 g, 11.04 mmol) was added in one portion and the resulting mixture was heated to 105° C. for 18 hours. The mixture was cooled to room temperature and the volatiles were removed in vacuo. The crude residue was loaded directly onto a silica-gel column and purified by elution with 95:5 mixture of hexanes/ethyl acetate v/v, increasing the polarity to 9:1 over time. The product was isolated as a white solid (410 mg, 1.31 mmol, 36%) and starting material was recovered (272 mg, 0.93 mmol, 25%). For 2-(4-Bromo-phenyl)-4-fluoro-2H-pyrazole-3-carboxylic acid ethyl ester: HPLC (254 nm): Method 3 Rt 2.97 min. MS (ESI) m/z 313.1 [M+H$^+$].

**[0454]** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H); 7.58 (d, J=9 Hz, 2H); 7.29 (d, J=9 Hz, 2H); 4.30 (q, J=7.1 Hz, 2H); 1.28 (t, J=7.1 Hz, 3H).

Step 6: 2-(4-Bromo-phenyl)-4-fluoro-2H-pyrazole-3-carboxylic acid

**[0455]** A stirred solution of 2-(4-bromo-phenyl)-4-fluoro-2H-pyrazole-3-carboxylic acid ethyl ester [Example 15, Step 5] (410 mg, 1.31 mmol) in THF (13 mL) was treated with LiOH 1 N aqueous solution (13 mL) and the resulting mixture was stirred at room temperature overnight. The reaction was deemed complete by thin layer chromatography and HPLC/MS. The reaction mixture was partitioned between ethyl acetate and 1 N aqueous HCl solution (100 mL v/v) and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was back-extracted with ethyl acetate (30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford the pure product as a white solid (347 mg, 1.22 mmol, 93%). HPLC (254 nm): Method 3 Rt 2.82 min. MS (ESI) m/z 285.1 [M+H$^+$].

Step 7: (R)-[2-(4-Bromo-phenyl)-4-fluoro-2H-pyrazol-3-yl]-carbamic acid 1-(2-chloro-phenyl)-ethyl ester

**[0456]** 2-(4-Bromo-phenyl)-4-fluoro-2H-pyrazole-3-carboxylic acid [Example 15, Step 6](347 mg, 1.22 mmol) was suspended in toluene (12 mL) and treated with triethylamine (205 μL, 1.46 mmol). The resulting solution was treated with diphenylphosphoryl azide (316 μL, 1.46 mmol) and heated to 65° C. (R)-1-(2-Chloro-phenyl)-ethanol (230 mg, 1.46 mmol) was added to the reaction mixture and the temperature was increased to 105° C. for 30 minutes, during which time vigorous gas evolution was observed. The reaction was brought to 65° C. and stirred at that temperature for 4 hours.

The reaction was deemed complete by HPLC/MS. After cooling, the volatiles were removed in vacuo and the crude residue was purified by silica gel chromatography, eluting with a hexanes/ethyl acetate gradient. Product isolated as a white solid (452 mg, 1.03 mmol, 85%). HPLC (254 nm): Method 3 Rt 3.16 min. MS (ESI) m/z 440.1 [M+H$^+$].

Step 8: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate

**[0457]** (R)-[2-(4-bromo-phenyl)-4-fluoro-2H-pyrazol-3-yl]-carbamic acid 1-(2-chloro-phenyl)-ethyl ester [Example 15, Step 7] (200 mg, 0.45 mmol) and 1-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclopropanecarboxamide [Example 15, Step 2] (196 mg, 0.68 mmol) were dissolved in acetonitrile (3 mL) and treated with a 2M $Na_2CO_3$ aqueous solution (1.5 mL). The resulting mixture was degassed under $N_2$ for 10 minutes, treated with $Pd[Ph_3P]_4$ (8 mg, 0.006 mmol) and heated to 80° C. for 6 hours, after which time reaction was deemed completed by LCMS. After cooling to room temperature, the reaction mixture was filtered through a pad of CELITE and rinsed with ethyl acetate. The filtrates were washed with water and brine. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated. The product was purified by silica gel chromatography, eluting with a hexanes/ethyl acetate gradient. The pure product was obtained as a tan solid. Yield=28 mg (12%). Method 3, Rt 3.07 min. MS (ESI) m/z 518.4 [M+H$^+$].

Example 16: (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate [Compound 16]

Step 1: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole

**[0458]** A suspension of 2-(p-bromophenyl)-2H-pyrazole-3-carboxylic acid [Example 3, Step 5] (100 g, 376 mmol) in dichloromethane (1880 mL) and N,N-dimethylformamide (1 mL) was stirred mechanically and cooled to 0° C. under an atmosphere of $N_2$. Oxalyl chloride (65.6 mL, 752 mmol) was added dropwise via addition funnel in approximately 30 minutes. The resulting suspension was warmed to room temperature and then heated to reflux. After 2 hours of reflux, LCMS showed complete conversion to the acid chloride. The reaction mixture was cooled to rt, and the volatiles were removed in vacuo to dryness. The acid chloride was obtained as a beige solid. This material was dissolved in ethyl acetate (940 mL) and treated with a solution of $NaN_3$ (48.88 g, 752 mmol) dissolved in $H_2O$ (940 mL). After stirring for 1 hour at rt, LCMS shows complete conversion to the acyl azide. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and evaporated at room temperature under vacuum. The acyl azide was obtained as a beige solid. This material was dissolved in toluene (1880 mL) with mechanical stirring. The reaction was heated to 100° C. for 1 hour and $N_2$ evolution was observed. Conversion to the isocyanate intermediate was monitored by LCMS after MeOH quenching. (1R)-1-(o-Chlorophenyl)-1-ethanol (64.77 g, 413.6 mmol) was added dropwise and the resulting mixture was stirred overnight at 65° C. The reaction was cooled. concentrated in vacuo to dryness. The crude is a thick amber oil. This oil was dissolved in $iPr_2O$ (500 mL) and stirred for 1 hour at rt. The thick beige precipitate was filtered, rinsed with $iPr_2O$ and air-dried. Obtained 97 g (61%) of pure product. The mother liquor was concentrated to dryness and the resulting oily residue was re-dissolved in $iPr_2O$ (200 mL) and stirred at rt overnight. The solids were filtered, rinsed with $iPr_2O$ and air dried. Obtained 10 g (6%). Overall yield=107 g (67%). Method 3, Rt 3.18 min. MS (ESI) m/z 422.1 [M+H$^+$].

Step 2: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole

**[0459]** A stirred solution of 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole [Example 16, Step 1] (50 g, 119 mmol) in acetonitrile (1190 mL) and acetic acid (119 mL) was treated with Selectfluor® (105.4 g, 297.5 mmol) and the resulting mixture was heated to 50° C. After 1.5 hours, LCMS indicates clean conversion to product. The reaction mixture was cooled and concentrated in vacuo. The crude residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine. Organics dried over anhydrous $MgSO_4$, filtered and evaporated. The thick amber oil was dissolved in $iPr_2O$ (300 mL) and stirred at room temperature. The precipitate was filtered under vacuum and air-dried to give 40 g (77%) of pure product. Method 3, Rt 3.38 min. MS (ESI) m/z 439.8 [M+H$^+$].

Step 3: 1-(4-bromo-3-fluorophenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide

**[0460]** 1-(4-Bromo-3-fluorophenyl)cyclopropanecarboxylic acid (5.18 g, 20.0 mmol) was suspended in dichloromethane (100 mL) and treated with a catalytic amount of N,N-dimethylformamide (3 drops) at room temperature. The reaction mixture was cooled to 0° C. with an ice/water bath. Oxalyl chloride (3.49 mL, 40.0 mmol) was added dropwise and the resulting mixture was stirred at 0° C. for 15 minutes and at room temperature for 30 minutes and then heated to reflux for 1.5 hours. An aliquot was dissolved in methanol and subjected to LCMS analysis, which indicated complete conversion to the corresponding acid chloride. The volatiles were removed under reduced pressure to yield the crude acid chloride as a white solid which was used immediately. A portion of the acid chloride (833 mg, 3.0 mmol) was dissolved in toluene and treated with triethylamine (2.1 mL, 15.0 mmol) and methylsulfonamide (1.43 g, 15.0 mmol). The resulting mixture was heated to reflux for 2 hours. The reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed with 1 N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude solid was triturated with diethyl ether and filtered. Product obtained as a beige solid. Yield=439 mg (44%). Method 3, Rt 2.60 min. MS (ESI) m/z 338.4 [M+H$^+$].

Step 4: 1-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide

**[0461]** 1-(4-bromo-3-fluorophenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide [Example 16, Step 3] (437 mg, 1.30 mmol) was dissolved in 1,4-dioxane (13 mL) and treated with potassium acetate (287 mg, 2.93 mmol) and pinacol diborane (826 mg, 3.25 mmol). The resulting mix-

ture was degassed under $N_2$ for 10 minutes. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (53 mg, 0.065 mmol) was added and the resulting mixture was heated to 95° C. for 16 hours. After cooling, the reaction mixture was filtered through a pad of CELITE, rinsed with ethyl acetate and concentrated. The crude residue was purified by silica-gel chromatography, eluting with a 1:1 v/v mixture of hexanes and ethyl acetate. The product was obtained as a white solid, after trituration from diethyl ether. Yield=273 mg (55%). Method 3, Rt 2.80 min. MS (ESI) m/z 384.5 [M+H$^+$].

Step 5: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-4-fluoro-2-{2'-fluoro-4'-[1-(methylsulfonylamino)carbonylcyclopropyl]-4-biphenylyl}-2H-pyrazole

**[0462]** A stirring mixture of 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 16, Step 2] (44 mg, 0.10 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (333 μL) and 1-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide [Example 16, Step 4] (57 mg, 0.15 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.005 mmol). The resulting mixture was heated to 85° C. and stirred for 6 hours at that temperature. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by preparative thin layer chromatography, eluting with a 90:10 v/v mixture of acetone and dichloromethane, respectively. Yield=8 mg (13%). Method 3, Rt 3.24 min. MS (ESI) m/z 615.2 [M+H$^+$].

Example 17: (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate [Compound 17]

**[0463]** A stirring mixture of 3-[(R)-1-Phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 3, Step 7] (37 mg, 0.092 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (333 μL) and 1-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide [Example 16, Step 4] (57 mg, 0.15 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.005 mmol). The resulting mixture was heated to 85° C. and stirred for 6 hours at that temperature. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by preparative thin layer chromatography, eluting with a 90:10 v/v mixture of acetone and dichloromethane, respectively. Yield=6 mg (11%). Method 3, Rt 3.34 min. MS (ESI) m/z 581.4 [M+H$^+$].

Example 18: (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate [Compound 18]

Step 1: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole

**[0464]** N-Chlorosuccinimide (155 mg, 1.16 mmol) was added to a stirring solution containing 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole [Example 16, Step 1] (486 mg, 1.16 mmol) in acetonitrile (6 mL) at room temperature. The resulting mixture was heated to 80° C. for 4 hours, after which time the reaction was deemed complete by LCMS. The reaction mixture was cooled to room temperature, concentrated in vacuo and purified directly via silica-gel column chromatography, eluting with a hexanes/ethyl acetate gradient. The product was obtained as a yellow oil, which solidified upon standing. Yield=328 mg (62%). Method 3, Rt 3.27 min. MS (ESI) m/z 455.8 [M+H$^+$].

Step 2: (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate

**[0465]** A stirring mixture of 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 18, Step 1] (45 mg, 0.10 mmol), 2:1 v/v mixture of toluene and ethanol (1 mL), 2M $Na_2CO_3$ aqueous solution (333 μL) and 1-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide [Example 16, Step 4] (57 mg, 0.15 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (6 mg, 0.005 mmol). The resulting mixture was heated to 85° C. and stirred for 6 hours at that temperature. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by preparative thin layer chromatography, eluting with a 90:10 v/v mixture of acetone and dichloromethane, respectively. Yield=4.8 mg (8%). Method 3, Rt 3.11 min. MS (ESI) m/z 631.7 [M+H$^+$].

Example 19: (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate [Compound 19]

Step 1: 1-(4-bromophenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide

**[0466]** 1-(p-Bromophenyl)cyclopropanecarboxylic acid (2.41 g, 10.0 mmol) was suspended in dichloromethane (50 mL) and treated with a catalytic amount of N,N-dimethylformamide (3 drops) at room temperature. The reaction mixture was cooled to 0° C. with an ice/water bath. Oxalyl chloride (1.75 mL, 20.0 mmol) was added dropwise and the resulting mixture was stirred at 0° C. for 15 minutes and at room temperature for 30 minutes and then heated to reflux for 1.5 hours. An aliquot was dissolved in methanol and subjected to LCMS analysis, which indicated complete conversion to the corresponding acid chloride. The volatiles were removed under reduced pressure to yield the crude acid chloride as a white solid which was used immediately. The acid chloride (2.60 g, 10.0 mmol) was dissolved in toluene (25 mL) and treated with triethylamine (7.01 mL, 50.0 mmol) and methylsulfonamide (4.75 g, 50.0 mmol). The resulting mixture was heated to reflux for 2 hours. The reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed with 1 N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and

evaporated. The crude solid was triturated with diisopropyl ether and filtered. Product obtained as a tan solid. Yield=997 mg (31%). Method 3, Rt 2.74 min. MS (ESI) m/z 318.3-319.8 [M+H$^+$].

Step 2: N-(methylsulfonyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxamide

**[0467]** 1-(4-bromophenyl)-N-(methylsulfonyl)cyclopropane-1-carboxamide [Example 19, Step 1] (997 mg, 3.13 mmol) was dissolved in 1,4-dioxane (30 mL) and treated with potassium acetate (690 mg, 7.04 mmol) and pinacol diborane (1.99 g, 7.83 mmol). The resulting mixture was degassed under $N_2$ for 10 minutes. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (128 mg, 0.157 mmol) was added and the resulting mixture was heated to 95° C. for 16 hours. After cooling, the reaction mixture was filtered through a pad of CELITE, rinsed with ethyl acetate and concentrated. The crude residue was purified by silica-gel chromatography, eluting with a hexanes and ethyl acetate gradient. The product was obtained as a white solid, after trituration from diethyl ether. Yield=1.00 g (88%). Method 3, Rt 2.95 min. MS (ESI) m/z 366.0 [M+H$^+$].

Step 3: (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate

**[0468]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 4, Step 1] (210 mg, 0.5 mmol), 2:1 v/v mixture of toluene and ethanol (5 mL), 2M $Na_2CO_3$ aqueous solution (1.67 mL) and N-(methylsulfonyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxamide [Example 19, Step 2] (219 mg, 0.6 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (29 mg, 0.025 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica-gel chromatography, eluting with a hexanes and ethyl acetate gradient. Product obtained as a white solid. Yield=140 mg (48%). Method 3, Rt 3.36 min. MS (ESI) m/z 579.4 [M+H$^+$].

Example 20: (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate [Compound 20]

**[0469]** A stirring mixture of 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 15, Step 5] (219 mg, 0.5 mmol), 2:1 v/v mixture of toluene and ethanol (5 mL), 2M $Na_2CO_3$ aqueous solution (1.67 mL) and N-(methylsulfonyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxamide [Example 19, Step 2] (219 mg, 0.6 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (29 mg, 0.025 mmol). The resulting mixture was heated to 85° C. and stirred for 16 hours at that temperature. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica-gel chromatography, eluting with a hexanes and ethyl acetate gradient. Product obtained as a white solid. Yield=110 mg (37%). Method 3, Rt 3.21 min. MS (ESI) m/z 597.4 [M+H$^+$].

Example 21: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate [Compound 21]

Step 1: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-[4'-(1-cyanocyclopropyl)-4-biphenylyl]-4-fluoro-2H-pyrazole

**[0470]** A stirring mixture of 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-4-fluoro-2H-pyrazole [Example 15, Step 5] (438 mg, 1.0 mmol), 2:1 v/v mixture of toluene and ethanol (10 mL), 2M $Na_2CO_3$ aqueous solution (3.3 mL) and 4-(1-cyanocyclopropyl)phenylboronic acid (243 mg, 1.3 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (58 mg, 0.05 mmol). The resulting mixture was heated to 85° C. and stirred for 3 hours at that temperature. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica-gel chromatography, eluting with a hexanes and ethyl acetate gradient. Yield=403 mg (81%). Method 3, Rt 3.20 min. MS (ESI) m/z 501.7 [M+H$^+$].

Step 2: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate

**[0471]** A stirred solution containing 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-{6-[p-(1-cyanocyclopropyl)phenyl]-3-pyridyl}-4-fluoro-2H-pyrazole [Example 21, Step 1] (50 mg, 0.10 mmol) in toluene (10 mL) was treated with dibutyltin(IV) oxide (27 mg, 0.10 mmol) and trimethylsilyl azide (36 μL, 0.27 mmol). The resulting mixture was heated to 100° C. for 16 hours and then cooled to room temperature and concentrated in vacuo. The crude product was purified by preparative thin layer chromatography, eluting with a 95:5 v/v mixture of dichloromethane and methanol, respectively. Yield=17 mg (31%). Method 3, Rt 3.29 min. MS (ESI) m/z 544.5 [M+H$^+$].

Example 22: (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate [Compound 22]

Step 1: 3-[(R)-1-Phenylethoxycarbonylamino]-4-chloro-2-[4'-(1-cyanocyclopropyl)-4-biphenylyl]-2H-pyrazole

**[0472]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 4, Step 1] (210 mg, 0.5 mmol), 2:1 v/v mixture of toluene and ethanol (5 mL), 2M $Na_2CO_3$ aqueous solution (1.7 mL) and 4-(1-cyanocyclopropyl)phenylboronic acid (112 mg, 0.6 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (29 mg, 0.025 mmol). The resulting mixture was heated to 85° C. and stirred for 3 hours at that temperature. The reaction mixture was cooled to

room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica-gel chromatography, eluting with a hexanes and ethyl acetate gradient. Product obtained as a white solid. Yield=173 mg (72%). Method 3, Rt 3.36 min. MS (ESI) m/z 483.5 [M+H$^+$].

Step 2: (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate

**[0473]** A stirred solution containing 3-[(R)-1-phenylethoxycarbonylamino]-4-chloro-2-[4'-(1-cyanocyclopropyl)-4-biphenylyl]-2H-pyrazole [Example 22, Step 1] (101 mg, 0.21 mmol) in toluene (1 mL) was treated with dibutyltin(IV) oxide (58 mg, 0.23 mmol) and trimethylsilyl azide (75 μL, 0.57 mmol). The resulting mixture was heated to 100° C. for 16 hours and then cooled to room temperature and concentrated in vacuo. The residue was dissolved in ethyl acetate, treated with 1 N HCl aqueous and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by C-18 reverse phase chromatography, eluting with a water and acetonitrile+0.1% TFA gradient. Yield=39 mg (35%). Method 3, Rt 3.07 min. MS (ESI) m/z 526.1 [M+H$^+$].

Example 23: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate [Compound 23]

Step 1: 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-4-chloro-2-[4'-(1-cyanocyclopropyl)-4-biphenylyl]-2H-pyrazole

**[0474]** A stirring mixture of 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 18, Step 1] (227 mg, 0.5 mmol), 2:1 v/v mixture of toluene and ethanol (5 mL), 2M $Na_2CO_3$ aqueous solution (1.7 mL) and 4-(1-cyanocyclopropyl)phenylboronic acid (112 mg, 0.6 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (29 mg, 0.025 mmol). The resulting mixture was heated to 85° C. and stirred for 3 hours at that temperature. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 1N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica-gel chromatography, eluting with a hexanes and ethyl acetate gradient. Product obtained as a white solid. Yield=189 mg (73%). Method 3, Rt 3.48 min. MS (ESI) m/z 517.3 [M+H$^+$].

Step 2: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate

**[0475]** A stirred solution containing 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-4-chloro-2-[4'-(1-cyanocyclopropyl)-4-biphenylyl]-2H-pyrazole [Example 23, Step 1] (108 mg, 0.21 mmol) in toluene (1 mL) was treated with dibutyltin(IV) oxide (58 mg, 0.23 mmol) and trimethylsilyl azide (75 μL, 0.57 mmol). The resulting mixture was heated to 100° C. for 16 hours and then cooled to room temperature and concentrated in vacuo. The residue was dissolved in ethyl acetate, treated with 1 N HCl aqueous and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by C-18 reverse phase chromatography, eluting with a water and acetonitrile+0.1% TFA gradient. Yield=36 mg (31%). Method 3, Rt 3.18 min. MS (ESI) m/z 560.1 [M+H$^+$].

Example 24: (R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate [Compound 24]

**[0476]** (R)-1-(4'-(4-chloro-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Example 4] (200 mg, 0.40 mmol) was co-evaporated twice with pyridine (10 mL) and dissolved in DMF (4.5 mL). The resulting solution was treated with pyridine (300 μL, 3.75 mmol) followed by dropwise addition of pentafluorophenyl trifluoroacetate (125 μL, 0.71 mmol). After 2 hours at room temperature, LCMS analysis indicates complete conversion to the corresponding pentafluorophenyl ester. The reaction mixture was diluted with ethyl acetate (30 mL) and treated with saturated $NaHCO_3$ aqueous solution. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was taken up in DMF (4 mL) and treated with sodium hydrogen cyanamide (77 mg, 1.2 mmol) at room temperature overnight. Next morning, reaction was diluted with ethyl acetate (30 mL) and treated with saturated $NaHCO_3$ aqueous solution. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The product was purified by preparative thin layer chromatography, eluting with a 90:10 v/v mixture of dichloromethane and methanol, respectively. Yield=36 mg (32%). Method 3, Rt 2.84 min. MS (ESI) m/z 526.5 [M+H$^+$].

Example 25: (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate [Compound 25]

Step 1: 1-(4-bromophenyl)-N-cyanocyclopropane-1-carboxamide

**[0477]** 1-(p-Bromophenyl)cyclopropanecarboxylic acid (2.41 g, 10.0 mmol) was suspended in dichloromethane (34 mL) and treated with a catalytic amount of N,N-dimethylformamide (2 drops) at room temperature. The reaction mixture was cooled to 0° C. with an ice/water bath. Oxalyl chloride (1.75 mL, 20.0 mmol) was added dropwise and the resulting mixture was stirred at 0° C. for 15 minutes and at room temperature for 30 minutes and then heated to reflux for 2 hours. An aliquot was dissolved in methanol and subjected to LCMS analysis, which indicated complete conversion to the corresponding acid chloride. The volatiles were removed under reduced pressure to yield the crude acid chloride as a white solid which was used immediately. The acid chloride (2.60 g, 10.0 mmol) was dissolved in DMF (30 mL) and a 10 mL aliquot of this solution was taken (3.3 mmol) and treated with sodium hydrogen cyanamide (640 mg, 10.0 mmol). The resulting mixture was stirred at room temperature overnight. The reaction was diluted with ethyl acetate, washed with 1 N HCl aqueous and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude solid product was used in the next step without any further purification. Product obtained as a solid. Yield=650 mg (74%). Method 3, Rt 2.68 min. MS (ESI) m/z 267.3 [M+H$^+$].

Step 2: N-cyano-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxamide

**[0478]** 1-(4-bromophenyl)-N-cyanocyclopropane-1-carboxamide [Example 25, Step 1](650 mg, 2.44 mmol) was dissolved in 1,4-dioxane (12 mL), treated with bis(pinacolato)diboron (1.94 g, 7.33 mmol), KOAc (720 mg, 7.33 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (193 mg, 0.32 mmol). The resulting mixture was heated to 100° C. overnight and then cooled to room temperature, filter through a pad of CELITE and rinsed with methanol. The filtrate was concentrated in vacuo. The crude material was purified by preparative think layer chromatography on silica gel, eluting with a 1:1 v/v mixture of hexanes and ethyl acetate. The product is a white solid. Yield=400 mg (53%). Method 3, Rt 2.86 min. MS (ESI) m/z 313.6 [M+H$^+$].

Step 3: (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate

**[0479]** A stirred suspension of 3-[(R)-1-(o-chlorophenyl) ethoxycarbonylamino]-2-(p-bromophenyl)-4-chloro-2H-pyrazole [Example 18, Step 1] (127 mg, 0.28 mmol), 1,4-dioxane (3 mL), 2 M aqueous solution of $Na_2CO_3$ (630 μL) and N-cyano-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxamide [Example 25, Step 2] (106 mg, 0.34 mmol) was degassed under nitrogen for 10 minutes and treated with Pd[$Ph_3P$]$_4$ (46 mg, 0.04 mmol). The resulting mixture was immersed in an oil bath with stirring at 95° C. for 12 hours. The reaction was cooled, transferred to a separatory funnel and diluted with ethyl acetate (50 mL). The mixture was carefully treated with 1 N aqueous HCl solution (20 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by preparative TLC plate (1000 μm), eluting with a 9:1 v/v dichloromethane/methanol mixture. The product was obtained as a white solid. Yield=18 mg (12%). HPLC (254 nm): Method 3, Rt 3.15 min. MS (ESI) m/z 560.5 [M+H$^+$].

Example 26: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate [Compound 26]

Step 1: (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy) carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid

**[0480]** A stirred suspension of (R)-[2-(4-bromo-phenyl)-4-fluoro-2H-pyrazol-3-yl]-carbamic acid 1-(2-chloro-phenyl)-ethyl ester [Example 15, Step 5] (88 mg, 0.2 mmol), 2:1 v/v toluene/ethanol (2 mL), 2 M aqueous solution of $Na_2CO_3$ (670 μL) and 1-[4-(dihydroxyboranyl)-3-fluoro-phenyl]cyclopropane-1-carboxylic acid (45 mg, 0.20 mmol) was degassed under nitrogen for 10 minutes and treated with Pd[$Ph_3P$]$_4$ (12 mg, 0.01 mmol). The resulting mixture was immersed in an oil bath with stirring at 90° C. for 12 hours. The reaction was cooled, transferred to a separatory funnel and diluted with ethyl acetate (50 mL). The mixture was carefully treated with 1 N aqueous HCl solution (20 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by preparative TLC plate (1000 μm), eluting with a 1:1 v/v hexanes/ethyl acetate mixture. The product was obtained as a white solid. Yield=40 mg (37%). HPLC (254 nm): Method 3, Rt 3.14 min. MS (ESI) m/z 538.3 [M+H$^+$].

Step 2: (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate

**[0481]** A stirring mixture containing (R)-1-(4'-(5-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-4-fluoro-1H-pyrazol-1-yl)-2-fluoro-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid [Example 26, step 1] (107 mg, 0.2 mmol) THF (1 mL) and N-hydroxysuccinimide (23 mg, 0.2 mmol) was treated with N,N'-dicyclohexylcarbodiimide (41 mg, 0.2 mmol) at room temperature. The resulting mixture was stirred for 3 hours, then the separated solids were filtered and the filtrate solution was added to a stirring solution of sodium hydrogen cyanamide (38 mg, 0.6 mmol) in water (1 mL). The resulting mixture was stirred for 2 days at room temperature. The reaction mixture was diluted with ethyl acetate (30 mL) and treated with 0.1 N HCl aqueous to pH ~3. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by preparative thin layer chromatography, eluting with a 90:10 v/v mixture of dichloromethane and methanol, respectively. Yield=36 mg (32%). Method 3, Rt 3.13 min. MS (ESI) m/z 561.9 [M+H$^+$].

Example 27: (R)-2-(4'-(5-(((1-(2-chlorophenyl) ethoxy)carbonyl)amino)-4-cyano-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid [Compound 27]

**[0482]** A mixture containing 2-(p-bromophenyl)-2-methylpropionic acid (66 mg, 0.27 mmol), tetrahydroxydiboron (109 mg, 1.22 mmol), KOAc (26 mg, 1.22 mmol) in ethanol (3 mL) was degassed under $N_2$ and then treated with XPhosPdG3 (6 mg, 0.007 mmol). This mixture was heated to 80° C. for 2 hours under magnetic stirring and then cooled to room temperature. This reaction was then treated sequentially with 3-[(R)-1-(o-chlorophenyl)ethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole-4-carbonitrile [Example 6, Step 1] (54 mg, 0.12 mmol), 2 M $K_2CO_3$ aqueous (270 μL) and XPhosPdG3 (2 mg, 0.0023). The resulting mixture was degassed with $N_2$ for 5 minutes and then heated to 80° C. for 16 hours. The reaction was cooled to room temperature, filtered through a pad of CELITE and rinsed with ethanol. The filtrates were concentrated in vacuo and the residue was purified by preparative thin layer chromatography, eluting with a 70:30 v/v toluene and acetone, respectively. The product was obtained as a white solid (12 mg, 19%). Method 3, Rt 3.23 min. MS (ESI) m/z 529.5 [M+H$^+$].

Example 28—(R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid [Compound 28]

Step 1: Methyl 2-methyl-2-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propionate

**[0483]** 2-(p-Bromophenyl)-2-methylpropionic acid (1.22 g, 5.0 mmol) was dissolved in methanol (20 mL), cooled to

−20° C. using ice water (2 parts) and salt (1 part). To this solution, thionyl chloride (1.45 mL, 20.0 mmol) was added dropwise. After completion of addition, the reaction was stirred for 15 minutes at −20° C. and then allowed to warm to room temperature over a period of 2 hours. LCMS indicated product formation. The reaction was concentrated in vacuo and the residue was partitioned between dichloromethane and an aqueous saturated $Na_2CO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to yield methyl 2-(p-bromophenyl)-2-methylpropionate (0.9 g, 3.5 mmol, 70%). This material was dissolved in 1,4-dioxane (20 mL), treated with bis(pinacolato)diboron (2.69 g, 10.1 mmol), KOAc (1.03 g, 10.5 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (328 mg, 0.44 mmol). The resulting mixture was heated to 100° C. overnight and then cooled to room temperature, filter through a pad of CELITE and rinsed with methanol. The filtrate was concentrated in vacuo. Part of the crude material was purified by preparative think layer chromatography on silica gel, eluting with hexanes. The product is a white solid. Yield=153 mg. Method 3, Rt 3.37 min. MS (ESI) m/z 305.8 [M+H$^+$].

Step 2: Methyl 2-(4'-{5-[(R)-1-phenylethoxycarbonylamino]-4-cyano-1H-pyrazol-1-yl}-4-biphenylyl)-2-methylpropionate

**[0484]** A stirring mixture of 3-[(R)-1-phenylethoxycarbonylamino]-2-(p-bromophenyl)-2H-pyrazole-4-carbonitrile [Example 5, Step 1] (58 mg, 0.14 mmol), 1,4-dioxane (2 mL), 2M $Na_2CO_3$ aqueous solution (315 μL) and methyl 2-methyl-2-[p-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propionate [Example 24, Step 1] (51 mg, 0.17 mmol) was degassed under $N_2$ for 10 minutes and treated with $Pd[Ph_3P]_4$ (23 mg, 0.02 mmol). The resulting mixture was heated to 95° C. overnight. The reaction mixture was cooled to room temperature, filtered through a pad of CELITE and rinsed with methanol. The filtrates were concentrated in vacuo and the crude residue was purified directly by preparative thin layer chromatography, eluting with 70:30 v/v mixture of hexanes and ethyl acetate, respectively. Yield=20 mg (28%). Method 3, Rt 3.17 min. MS (ESI) m/z 509.3 [M+H$^+$].

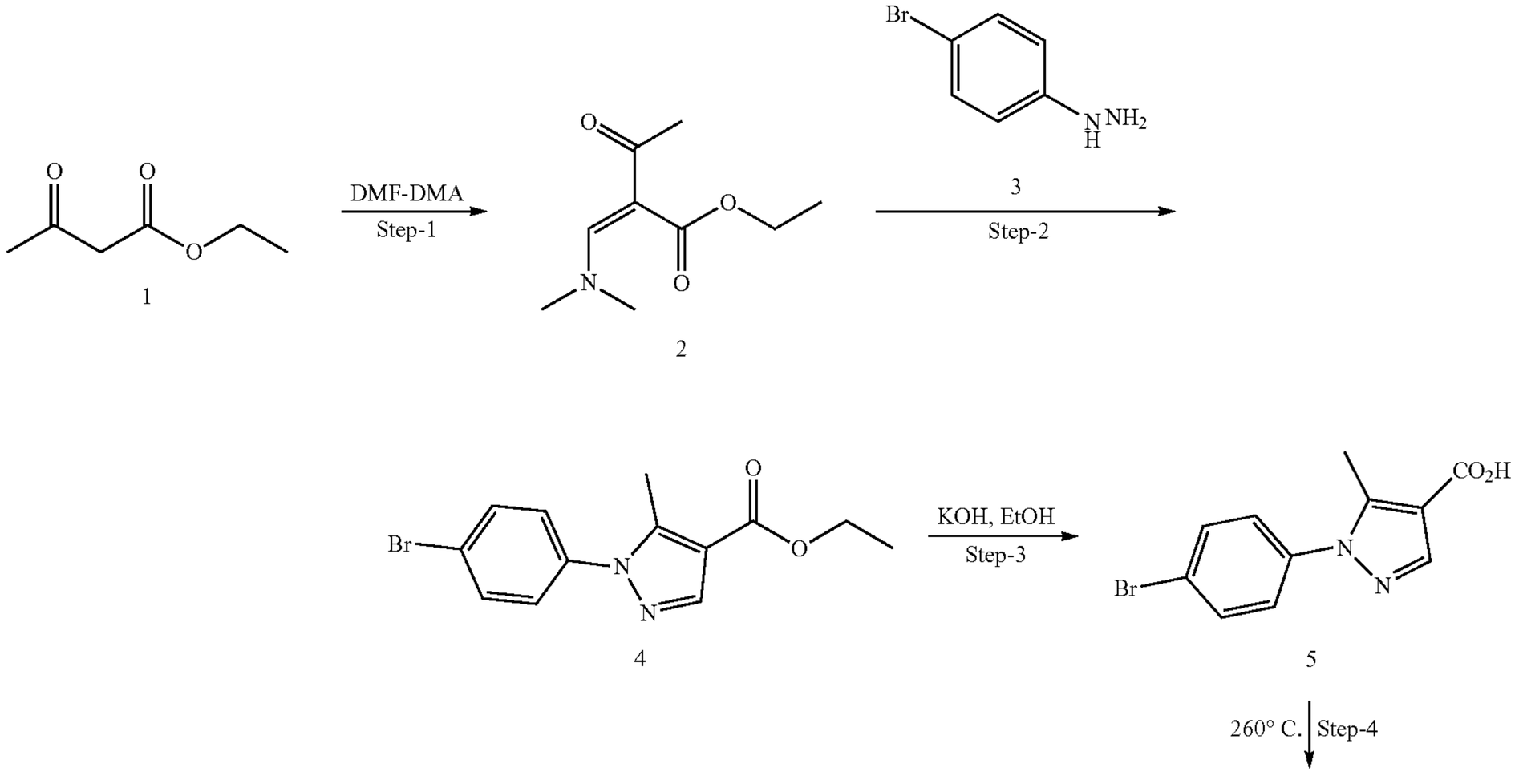
Step 3: (R)-2-(4'-(4-cyano-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-2-methylpropanoic acid

**[0485]** Methyl 2-(4'-{5-[(R)-1-phenylethoxycarbonylamino]-4-cyano-1H-pyrazol-1-yl}-4-biphenylyl)-2-methylpropionate [Example 28, Step 1] (18 mg, 0.03 mmol) was dissolved in THF (1 mL) and treated with a 1 M LiOH aqueous solution (1 mL) and the resulting mixture was stirred at room temperature overnight. Reaction progress was monitored by thin layer chromatography (30% ethyl acetate in hexanes). The reaction was treated with 1 M aqueous HCl solution (5 mL) and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude residue was purified by preparative thin layer chromatography, eluting with a 70:30 v/v mixture of toluene and acetone, respectively. The product was obtained as a white solid. Yield=15 mg (quant.). Method 3, Rt 2.93 min. MS (ESI) m/z 495.8 [M+H$^+$].

**[0486]** Compounds of Table 1 and derivatives thereof are prepared according to procedures outlined for compounds 1-28. The heterocyclic amines or esters required to assemble the corresponding carbamates were prepared based on methods described in citations 1-19.

**[0487]** Certain pyrazole substitutions are prepared following construction of the appropriate aryl pyrazole (8, Scheme 1). Direct flurorination, chlorination or trifluoromethylation provides arylbromide (9), intermediates suitable for further modification to compounds of the present invention according to procedures described for examples 1-28.

Scheme 1



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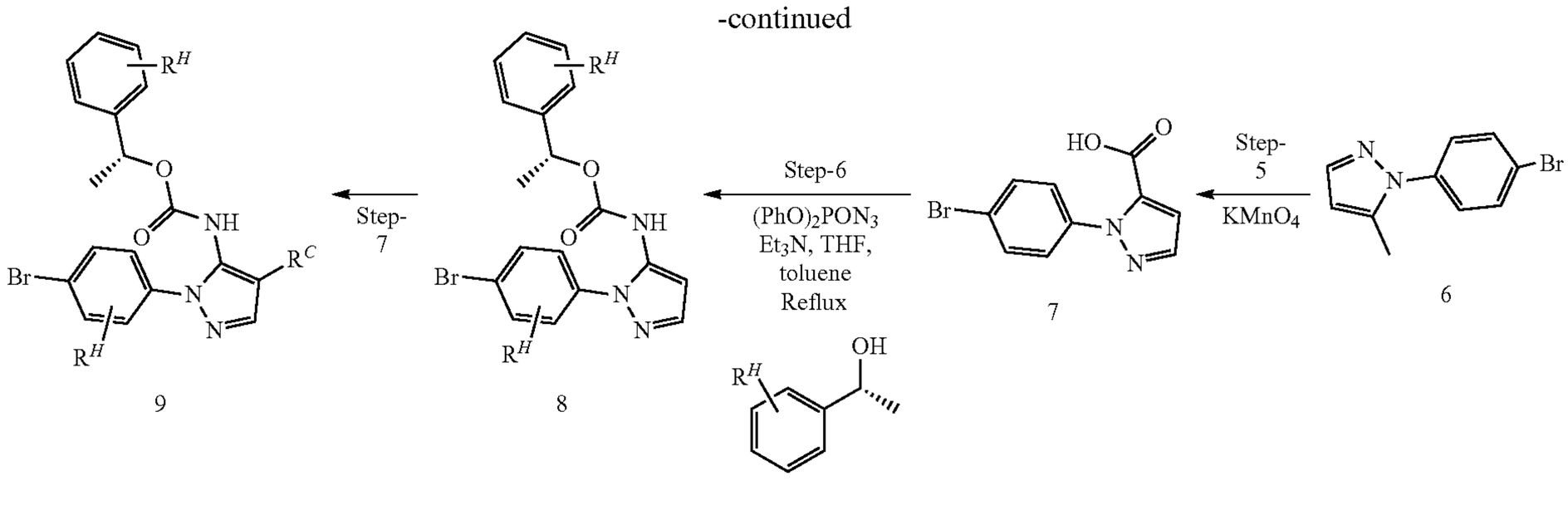
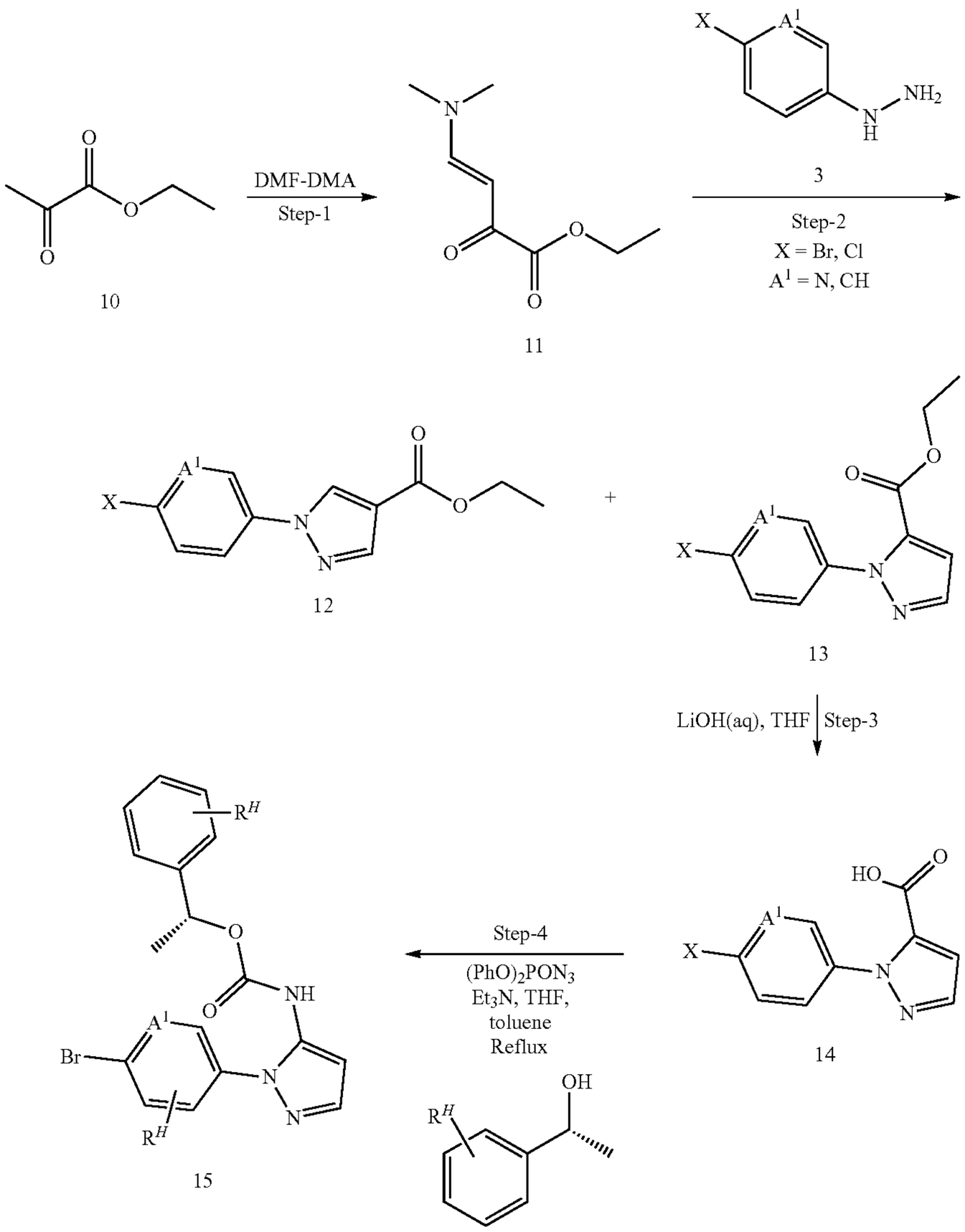


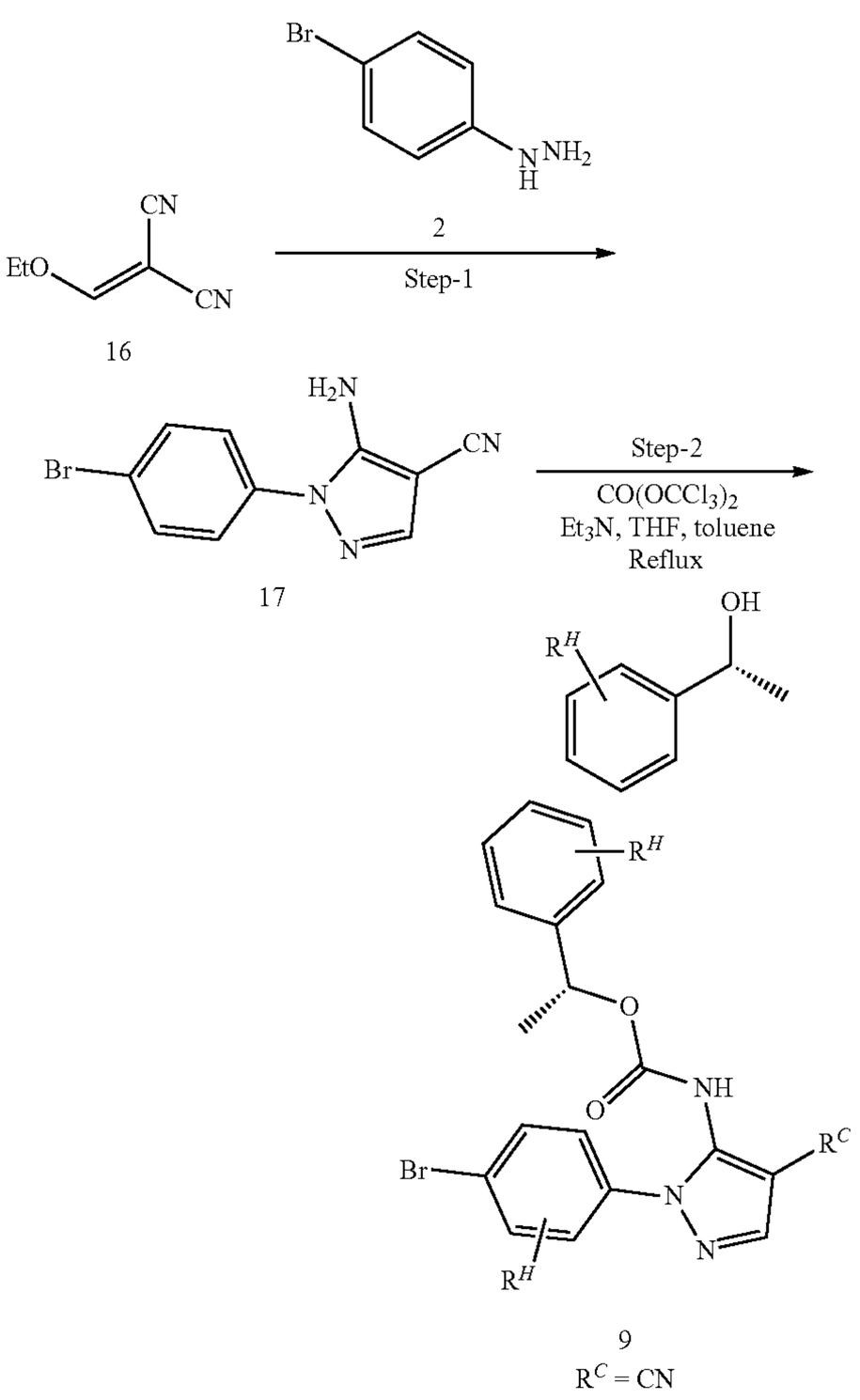

**[0488]** Alternatively, Core pyrazole (8) may be prepared according to the approach depicted in Scheme 2:

Scheme 2



**[0489]** Where the requirement for $R^C$ as cyano is concerned, the corresponding core cyanopyrazole (9) is prepared according to the steps described in Scheme 3:

Scheme 3




Example 29. Receptor Binding Assays

**[0490]** Binding affinity of compounds of Formula I-III were determined based on their ability to displace tritiated lysophosphatidic acid ([$^3$H]-LPA) from CHO cells expressing LPA1R in a protocol similar to that described in reference 17. In a 96 well format, CHO cells expressing human LPA1R [Cerep] were treated with [$^3$H]-LPA (2 nM). Test compounds were added in increasing concentration to each well and incubated at room temperature for 90 minutes. At this time the plates were washed and the wells counted for radioactivity. Results were compared to a control in which cells were treated with [$^3$H]-LPA in the presence of 10 μM unlabeled LPA. The specific ligand binding to the receptors was defined as the difference between the total binding and the nonspecific binding determined in the presence of an excess of unlabeled ligand. The results were expressed as a percent of control specific binding ((measured specific binding/control specific binding)×100) and as a percent inhibition of control specific binding (100-((measured specific binding/control specific binding)×100)) obtained in the presence of the test compounds. The $IC_{50}$ value (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficient (nH) were determined by non-linear regression analysis of the competition curve generated with mean replicate values using Hill equation curve fitting (Y=D+[(A−D)/(1+(C/C50)nH)], where Y=specific binding, D=minimum specific binding, A=maximum specific binding, C=compound concentration, C50=IC50, and nH=slope factor). This analysis was performed using a software developed at Cerep (Hill software) and validated by comparison with data generated by the commercial software SigmaPlot® 4.0 for Windows® (© 1997 by SPSS Inc.). The inhibition constant (Ki) was calculated using the Cheng Prusoff equation (Ki=IC50/(1+(L/KD)), where L=concentration of radioligand in the assay, and KD=affinity of the radioligand for the receptor). A scatchard plot was used to determine the Kd.

Example 30. Calcium Flux Assay

**[0491]** Inhibition of LPA-stimulated $Ca^{2+}$ flux was used to assess compound potency using FLIPR technology in a 96 well plate format. The assay buffer used was a modified Hanks Balanced Salt Solution (HBSS) where HBSS was supplemented to contain 20 mM HEPES and 2.5 mM Probenecid at pH7.4 (Millipore, GPCR Profiler®). LPA1R expressing cells (Millipore) were plated and prepared 24 hours prior to assay of test articles. $Ca^{2+}$ ion flux was assessed from fluorescence of a Fluo-based No Wash $Ca^{2+}$ dye. Antagonist data are generated from plates with LPA concentrations sufficient to generate 80% efficacy [$EC_{80}$]. Percentage inhibition was calculated from a reduction of efficacy according to concentration of compounds of Formula I-VI. For dose responses the inhibition data was used to calculate compound $IC_{50}$.

**[0492]** The agonist assay was conducted on a FLIPR$^{TETRA}$ instrument where the test compound(s), vehicle controls, and reference agonist were added to the assay plate after a fluorescence baseline was established. The agonist assay was a total of 180 seconds and was used to assess each compound's ability to activate each GPCR assayed. Upon completion of the agonist assay, the assay plate was removed from the FLIPR$^{TETRA}$ and incubated at 25° C. for seven (7) minutes. After the incubation period, the assay plate was placed back in the FLIPR$^{TETRA}$ and the antagonist assay was initiated.

**[0493]** Antagonist Assay: Using $EC_{80}$ potency values determined during the agonist assay, all pre-incubated sample compound wells were challenged with $EC_{80}$ concentration of reference agonist after establishment of a fluorescence baseline. The antagonist assay was conducted using the same assay plate that was used for the agonist assay. The antagonist assay was conducted on a FLIPR$^{TETRA}$ instrument where 9 vehicle controls and $EC_{80}$ concentration of reference agonist were added to appropriate wells. The antagonist assay was a total of 180 seconds and was used to assess each compound's ability to inhibit each GPCR assayed.

**[0494]** Data Processing: All assay plate data were subjected to appropriate baseline corrections. After baseline corrections were applied, maximum fluorescence values were exported and data processed to calculate percentage activation (relative to Emax reference agonist and vehicle control values), percentage inhibition (relative to EC80 and

vehicle control values), and additional statistical values (i.e. Z', percentage variation between replicate data values) to assess the quality of each plate. Where assay plate data were rejected, additional experiments were conducted. All dose response curves were generated using GraphPad Prism. The curves were fit by utilizing "Sigmoidal Dose Response (Variable Slope)" equation where the bottom parameter was fixed to "0." Where appropriate, the top parameter was fixed to "100" to better predict potency values when a full curve was not generated by the concentrations assayed.

**[0495]** Antagonist activity data for representative compounds prepared according to the synthetic methods disclosed herein are presented in Table 2.

TABLE 2

In vitro biological data for representative compounds of Formula I-III
Unless otherwise noted, compounds that were tested had an $IC_{50}$ of less than 50 μM in the LPA1R $Ca^{2+}$ flux functional assay.

| Compound | LPA1 R Antagonist Activity | Example Number | LPA1 R Antagonist Activity |
|---|---|---|---|
| 1 | A | 15 | A |
| 2 | A | 16 | A |
| 3 | A | 17 | A |
| 4 | A | 18 | A |
| 5 | A | 19 | A |
| 6 | A | 20 | A |
| 7 | A | 21 | C |
| 8 | A | 22 | A |
| 9 | A | 23 | C |
| 10 | A | 24 | C |
| 11 | A | 25 | C |
| 12 | A | 26 | A |
| 13 | A | 27 | A |
| 14 | A | 28 | A |

**[0496]** Unless otherwise noted, compounds that were tested had an $IC_{50}$ of less than 50 μM in the LPA1R $Ca^{2+}$ flux functional assay. A=less than 0.3 μM; B=greater than 0.3 μM and less than 1 μM; C=greater than 1 μM and less than 50 μM; D=greater than 50 μM

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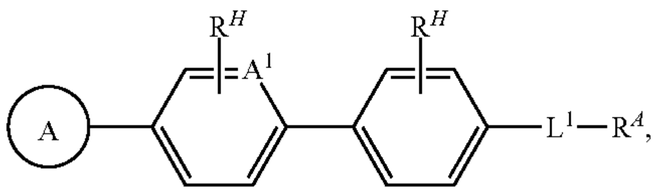
**1**. A compound having the structure of Formula I

Formula I

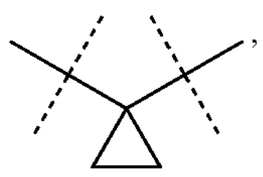


or a pharmaceutically acceptable salt thereof,

wherein $R^A$ is $—CO_2H$, tetrazolyl, $—C(=O)NH_2$, $—C(=O)NHR^B$, —CONHCN, $—C(=O)NHSO_2R^B$ or $—C(=O)NHCH_2CH_2SO_3H$;

$R^B$ is a substituted or unsubstituted $C_1$-$C_4$ alkyl;

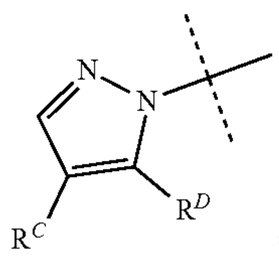
$L^1$ is a substituted or unsubstituted saturated $C_1$-$C_6$ alkylene, or $L^1$ is $—CH_2—$,



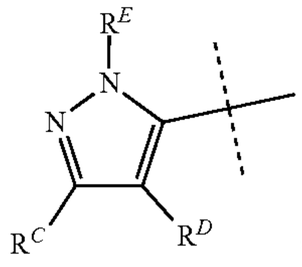
or dimethylmethane;

$A^1$ is N or C;

Ring A has the structure of one of:

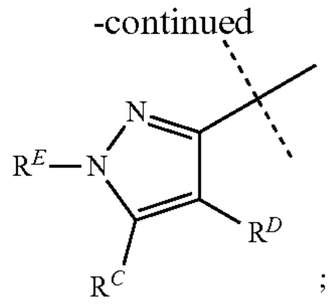


,



, and

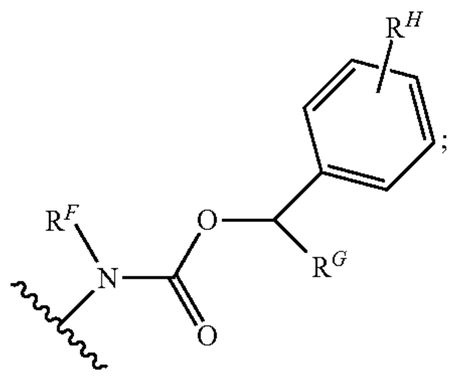
-continued



;

$R^C$ is —CN, —F, —Cl, or $C_1$-$C_4$ fluoroalkyl;

$R^D$ is $—N(R^F)—C(=O)XCH(R^G)—CY$, wherein X is O and CY is unsubstituted phenyl or Phenyl substituted with one $R^H$:



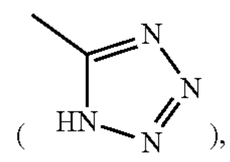
;

$R^E$, $R^F$ and $R^G$ independently are —H or saturated $C_1$-$C_4$ alkyl or $R^E$ and $R^F$ independently are —H or saturated $C_1$-$C_4$ alkyl and one $R^G$ is saturated $—C_1$-$C_4$ alkyl and is taken together with the $R^H$ phenyl moiety of the Ring A $R^D$ substituent and the carbon atom to which $R^G$ and said phenyl moiety is attached to define a substituted or unsubstituted carbocycle, and the other $R^G$, if present, is as defined for $R^E$; and

each $R^H$ is independently absent, a halogen, or substituted or unsubstituted saturated $C_1$-$C_4$ alkyl.

**2**. The compound according to claim **1**, wherein:

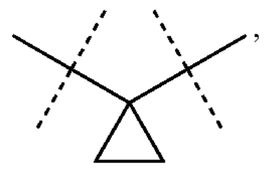
$R^A$ is tetrazolyl



,

$—C(=O)NH_2$, —CONHCN or $—C(=O)NHSO_2R^B$;

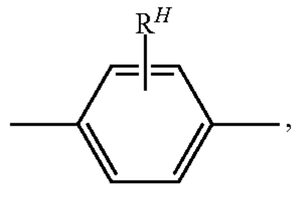
$L^1$ is $—CH_2—$,



,

or dimethylmethane;

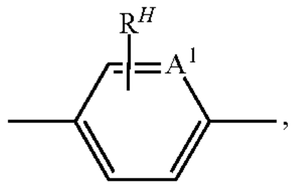
in the ring



,

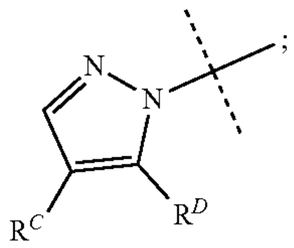
$R^H$ is absent, a halogen, or $—CH_3$;

in the ring



$A^1$ is C or N and $R^H$ is —H;

Ring A has the structure of

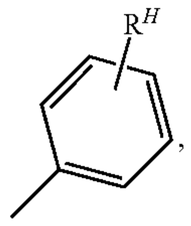


$R^C$ is —F, —Cl, or —CN;

$R^F$ is —H;

$R^G$ is —$CH_3$ in an R configuration; and

in the CY ring

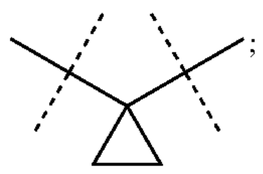


$R^H$ is absent or a halogen.

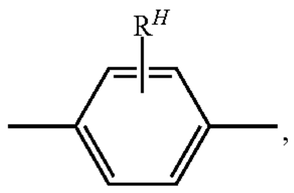
**3**. The compound according to claim **2**, wherein:

$R^A$ is —C(═O)$NHSO_2R^B$;

$L^1$ is

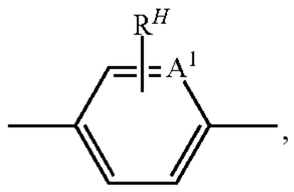


in the ring



$R^H$ is absent;

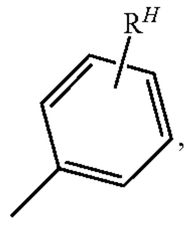
in the ring



$A^1$ is N and $R^H$ is absent;

$R^C$ is —F or —Cl; and

in the CY ring



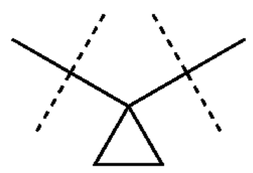
$R^H$ is —Cl.

**4**. (canceled)

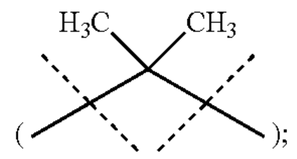
**5**. The compound according to claim **2**, wherein

$R^A$ is —C(═O)$NHSO_2R^B$

$L^1$ is

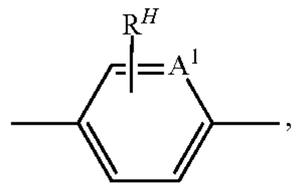


or dimethylmethane



$R^C$ is —F or —CN and

in the ring

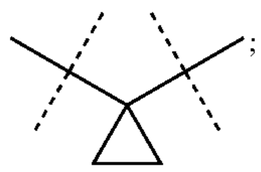


$A^1$ is C and $R^H$ is absent.

**6**. (canceled)

**7**. The compound according to claim **2**, wherein $R^A$ is —C(═O)$NHSO_2R^B$, wherein $R^B$ is $CH_3$; and

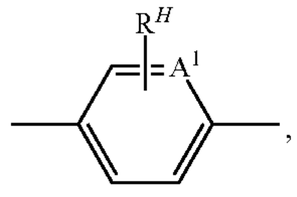
$L^1$ is



and

$R^C$ is —Cl; and

in the ring



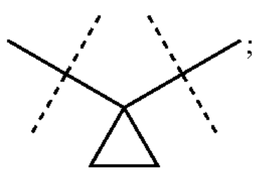
$A^1$ is C and $R^H$ is absent.

**8**. (canceled)

**9**. The compound according to claim **2**, wherein:

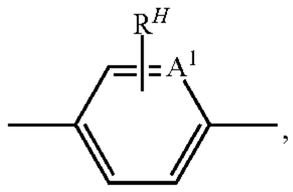
$R^A$ is —C(═O)$NH_2$;

$L^1$ is



$R^C$ is —F; and

in the ring



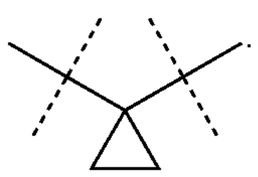
$A^1$ is C and $R^H$ is absent.

**10**. The compound according to claim **9**, wherein the compound is (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate.

**11**. The compound according to claim **2**, wherein:

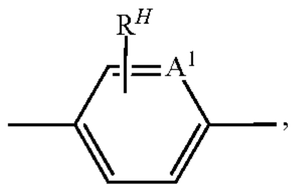
$R^A$ is —C(═O)$NHSO_2R^B$, wherein $R^B$ is —$CH_3$; and

$L^1$ is



$R^C$ is —F and

in the ring

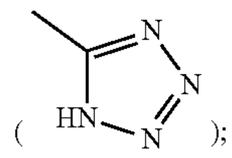


$A^1$ is C and $R^H$ is absent.

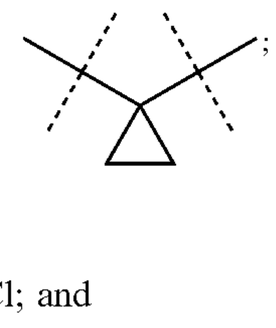
**12**. The compound according to claim **11**, wherein the compound is (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, or (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate,

**13**. The compound according to claim **2**, wherein:

$R^A$ is tetrazolyl



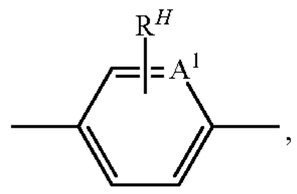
$L^1$ is



and

$R^C$ is —F or —Cl; and

in the ring



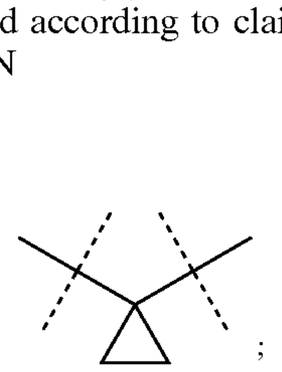
$A^1$ is C and $R^H$ is —H.

**14**. The compound according to claim **13**, wherein the compound is (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate or (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate.

**15**. The compound according to claim **2**, wherein:

$R^A$ is —CONHCN

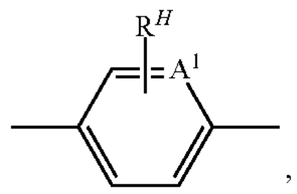
$L^1$ is



and

$R^C$ is —F or —Cl; and

in the ring



$A^1$ is C and $R^H$ is absent.

**16**. The compound according to claim **15** wherein the compound is (R)-1-phenylethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-

1H-pyrazol-5-yl)carbamate, or (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(cyanocarbamoyl)cyclopropyl)-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate.

**17**. The compound according to claim **2** wherein the compound is (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate.

**18**. The compound according to claim **1**, wherein $R^G$ is in an R or S configuration.

**19**. A pharmaceutical composition comprising:

the compound according to claim **1**; and

at least one pharmaceutically acceptable excipient.

**20**. A method for treating a lysophosphatidic acid-dependent disease or condition in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of the compound according to claim **1**.

**21**. The method according to claim **20**, wherein the lysophosphatidic acid-dependent disease or condition is diabetic nephropathy or nonalcoholic steatohepatitis (NASH).

**22**. A compound according to claim **1**, selected from the group consisting of (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-carbamoylcyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-fluoro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-chloro-1-(2'-fluoro-4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (4-chloro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (4-fluoro-1-(4'-(1-((methylsulfonyl)carbamoyl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-fluoro-1H-pyrazol-5-yl)carbamate, (R)-1-phenylethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, (R)-1-(2-chlorophenyl)ethyl (1-(4'-(1-(1H-tetrazol-5-yl)cyclopropyl)-[1,1'-biphenyl]-4-yl)-4-chloro-1H-pyrazol-5-yl)carbamate, 3-[(R)-1-Phenylethoxycarbonylamino]-4-chloro-2-{4'-[1-(cyanoamino)carbonylcyclopropyl]-4-biphenylyl}-2H-pyrazole, 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-4-chloro-2-{4'-[1-(cyanoamino)carbonylcyclopropyl]-4-biphenylyl}-2H-pyrazole, and 3-[(R)-1-(o-Chlorophenyl)ethoxycarbonylamino]-2-{4'-[1-(cyanoamino)carbonylcyclopropyl]-2'-fluoro-4-biphenylyl}-4-fluoro-2H-pyrazole.

* * * * *