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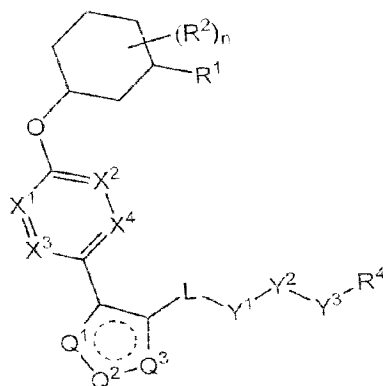
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(54) Titre : ACIDES CARBAMOYLE CYCLOHEXYLIQUES A LIAISON N PYRAZOLE UTILISES EN TANT QU'ANTAGONISTES DE LPA

(54) Title: PYRAZOLE N-LINKED CARBAMOYL CYCLOHEXYL ACIDS AS LPA ANTAGONISTS



(I)

(57) **Abrégé/Abstract:**

The present invention provides compounds of Formula (I) or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein X^1 , X^2 , X^3 , and X^4 are each independently CR^6 or N; provided that no more than two of X^1 , X^2 , X^3 , or X^4 are N; Q^2 is N or NR^{5a} ; one of Q^1 and Q^3 is CR^5 , and the other is N or NR^{5a} ; and the dashed circle denotes optional bonds forming an aromatic ring; Y^1 is O or NR^3 ; Y^2 is $-CO-$, $-SO_2-$, or $-S(O)(NH)-$; Y^3 is O or NR^{4a} ; provided that (1) Y^1 and Y^3 are not both O, and (2) when Y^2 is $C(O)$, Y^1 is not O; L is a covalent bond or C_{1-4} alkylene substituted with 0 to 4 R^7 ; R^1 is $(-CH_2)_aR^9$; a is an integer of 0 or 1; R^2 is each independently halo, cyano, hydroxyl, amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkoxyalkyl, haloalkoxyalkyl, or haloalkoxy; n is an integer of 0, 1, or 2; R^3 and R^{4a} are independently hydrogen, C_{1-6} alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R^4 is C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} deuterated alkyl, C_{1-10} alkenyl, C_{3-8} cycloalkyl, 6 to 10-membered aryl, 3 to 8-membered heterocyclyl, $-(C_{1-6}$ alkylene)-(C3-8 cycloalkyl), $-(C_{1-6}$ alkylene)-(6 to 10-membered aryl), $-(C_{1-6}$ alkylene)-(3 to 8-membered heterocyclyl), or $-(C_{1-6}$ alkylene)-(5 to 6-membered heteroaryl); wherein each of the alkyl, alkylene, alkenyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, by itself or as part of other moiety, is independently substituted with 0 to 3 R; or alternatively, R^3 and R^4 , taken together with the N and O atoms which they are attached, form a 4 to 9-membered heterocyclic ring moiety which is substituted with 0 to 3 R^8 ; or alternatively, $(R^3$ and $R^{5a})$ or $(R^3$ and $R^5)$, taken together with the atoms to which they are attached, form a 5 to 8-membered heterocyclic ring moiety which is substituted with 0 to 3 R^8 ; R^{5a} is hydrogen, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R^5 and R^6 are each independently hydrogen,

(57) Abrégé(suite)/Abstract(continued):

halo, cyano, hydroxyl, amino, alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R^7 is halo, oxo, cyano, hydroxyl, amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R^8 are each independently deuterium, halo, hydroxyl, amino, cyano, C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5 to 6-membered heteroaryl; or alternatively, two R^8 , taken together with the atom(s) to which they are attached, form a 3 to 6-membered carbocyclic ring or a 3 to 6-membered heterocyclic ring each of which is independently substituted with 0 to 3 R^{12} ; R^9 is selected from -CN, -C(O)OR¹⁰, -C(O)NR^{11a}R^{11b}, -CO-NH-CO-R^e, -CO-NH-SO₂-R^e, -CO-NH-SO-R^e, -SO₂-OH, -SO₂-NH-CO-R^e, -P(O)(OH)₂, tetrazol-5-yl, -CH₂-CO-NH-CO-R^e, -CH₂-CO-NH-SO₂-R^e, -CH₂-CO-NH-SO-R^e, -CH₂-SO₂-OH, -CH₂-SO₂-NH-CO-R^e, -CH₂-P(O)(OH)₂, tetrazol-5-ylmethylene; R^e is C_{1-6} alkyl, C_{3-6} cycloalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, or haloalkoxyalkyl; R^{10} is hydrogen or C_{1-10} alkyl; and R^{11a} and R^{11b} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; and R^{12} is halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5 to 6-membered heteroaryl. These compounds are selective LPA receptor inhibitors.

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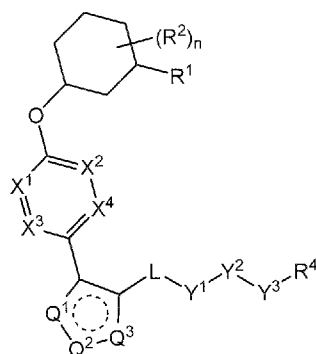
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(54) Title: PYRAZOLE N-LINKED CARBAMOYL CYCLOHEXYL ACIDS AS LPA ANTAGONISTS



(I)

(57) **Abstract:** The present invention provides compounds of Formula (I) or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein X¹, X², X³, and X⁴ are each independently CR⁶ or N; provided that no more than two of X¹, X², X³, or X⁴ are N; Q² is N or NR^{5a}, one of Q¹ and Q³ is CR⁵, and the other is N or NR^{5a}, and the dashed circle denotes optional bonds forming an aromatic ring; Y¹ is O or NR³; Y² is -CO-, -SO₂-, or -S(O)(NH)-; Y³ is O or NR^{4a}, provided that (1) Y¹ and Y³ are not both O, and (2) when Y² is C(O), Y¹ is not O; L is a covalent bond or C₁₋₄ alkylene substituted with 0 to 4 R⁷; R¹ is (-CH₂)_aR⁹; a is an integer of 0 or 1; R² is each independently halo, cyano, hydroxyl, amino, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkoxyalkyl, haloalkoxyalkyl, or haloalkoxy; n is an integer of 0, 1, or 2; R³ and R^{4a} are independently hydrogen, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R⁴ is C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterated alkyl, C₁₋₁₀ alkenyl, C₃₋₈ cycloalkyl, 6 to 10-membered aryl, 3 to 8-membered heterocyclyl, -(C₁₋₆ alkylene)-(C₃₋₈ cycloalkyl), -(C₁₋₆ alkylene)-(6 to 10-membered aryl), -(C₁₋₆ alkylene)-(3 to 8-membered heterocyclyl), or -(C₁₋₆ alkylene)-(5 to 6-membered heteroaryl); wherein each of the alkyl, alkylene, alkenyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, by itself or as part of other moiety, is independently substituted with 0 to 3 R; or alternatively, R³ and R⁴, taken together with the N and O atoms which they are attached, form a 4 to 9-membered heterocyclic ring moiety which is substituted with 0 to 3 R⁸; or alternatively, (R³ and R^{5a}) or (R³ and R⁵), taken together with the atoms to which they are attached to, form a 5 to 8-membered heterocyclic ring moiety which is substituted with 0 to 3 R⁸; R^{5a} is hydrogen, C₁₋₆ alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R⁵ and R⁶ are each independently hydrogen, halo,

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Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*

Published:

- *with international search report (Art. 21(3))*

cyano, hydroxyl, amino, alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R⁷ is halo, oxo, cyano, hydroxyl, amino, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; R⁸ are each independently deuterium, halo, hydroxyl, amino, cyano, C₁₋₆ alkyl, C₁₋₆ deuterated alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5 to 6-membered heteroaryl; or alternatively, two R⁸, taken together with the atom(s) to which they are attached, form a 3 to 6-membered carbocyclic ring or a 3 to 6-membered heterocyclic ring each of which is independently substituted with 0 to 3 R¹²; R⁹ is selected from -CN, -C(O)OR¹⁰, -C(O)NR^{11a}R^{11b}, -CO-NH-CO-R^e, -CO-NH-SO₂-R^e, -CO-NH-SO₂-R^e, -SO₂-OH, -SO₂-NH-CO-R^e, -P(O)(OH)₂, tetrazol-5-yl, -CH₂-CO-NH-CO-R^e, -CH₂-CO-NH-SO₂-R^e, -CH₂-CO-NH-SO₂-R^e, -CH₂-SO₂-OH, -CH₂-SO₂-NH-CO-R^e, -CH₂-P(O)(OH)₂, tetrazol-5-ylmethylene; R_e is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, or haloalkoxyalkyl; R¹⁰ is hydrogen or C₁₋₁₀ alkyl; and R^{11a} and R^{11b} are each independently hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; and R¹² is halo, cyano, hydroxyl, amino, C₁₋₆ alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5 to 6-membered heteroaryl. These compounds are selective LPA receptor inhibitors.

PYRAZOLE N-LINKED CARBAMOYL CYCLOHEXYL ACIDS AS LPA
ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the priority benefit of U.S. Provisional Application No. 62/607,541, filed December 19, 2017; the entire content of which is herein incorporated by reference.

FIELD OF THE INVENTION

10 The present invention relates to novel substituted pyrazole compounds, compositions containing them, and methods of using them, for example, for the treatment of disorders associated with one or more of the lysophosphatidic acid (LPA) receptors.

BACKGROUND OF THE INVENTION

15 Lysophospholipids are membrane-derived bioactive lipid mediators, of which one of the most medically important is lysophosphatidic acid (LPA). LPA is not a single molecular entity but a collection of endogenous structural variants with fatty acids of varied lengths and degrees of saturation (Fujiwara et al., *J Biol. Chem.*, **2005**, *280*, 35038-35050). The structural backbone of the LPAs is derived from glycerol-based
20 phospholipids such as phosphatidylcholine (PC) or phosphatidic acid (PA).

The LPAs are bioactive lipids (signaling lipids) that regulate various cellular signaling pathways by binding to the same class of 7-transmembrane domain G protein-coupled (GPCR) receptors (Chun, J., Hla, T., Spiegel, S., Moolenaar, W., Editors, *Lysophospholipid Receptors: Signaling and Biochemistry*, **2013**, Wiley; ISBN: 978-0-
25 470-56905-4 & Zhao, Y. et al, *Biochim. Biophys. Acta (BBA)-Mol. Cell Biol. Of Lipids*, **2013**, *1831*, 86–92). The currently known LPA receptors are designated as LPA₁, LPA₂, LPA₃, LPA₄, LPA₅ and LPA₆ (Choi, J. W., *Annu. Rev. Pharmacol. Toxicol.*, **2010**, *50*, 157-186; Kihara, Y., et al, *Br. J. Pharmacol.*, **2014**, *171*, 3575-3594).

The LPAs have long been known as precursors of phospholipid biosynthesis in
30 both eukaryotic and prokaryotic cells, but the LPAs have emerged only recently as signaling molecules that are rapidly produced and released by activated cells, notably platelets, to influence target cells by acting on specific cell-surface receptors (see, e.g.,

Moolenaar et al., *BioEssays*, **2004**, *26*, 870-881, and van Leewen et al., *Biochem. Soc. Trans.*, **2003**, *31*, 1209-1212). Besides being synthesized and processed to more complex phospholipids in the endoplasmic reticulum, LPAs can be generated through the hydrolysis of pre-existing phospholipids following cell activation; for example, the sn-2 position is commonly missing a fatty acid residue due to deacylation, leaving only the sn-1 hydroxyl esterified to a fatty acid. Moreover, a key enzyme in the production of LPA, autotaxin (lysoPLD/NPP2), may be the product of an oncogene, as many tumor types up-regulate autotaxin (Brindley, D., *J. Cell Biochem.* **2004**, *92*, 900-12). The concentrations of LPAs in human plasma & serum as well as human bronchoalveolar lavage fluid (BALF) have been reported, including determinations made using sensitive and specific LC/MS & LC/MS/MS procedures (Baker et al. *Anal. Biochem.*, **2001**, *292*, 287-295; Onorato et al., *J. Lipid Res.*, **2014**, *55*, 1784-1796).

LPA influences a wide range of biological responses, ranging from induction of cell proliferation, stimulation of cell migration and neurite retraction, gap junction closure, and even slime mold chemotaxis (Goetzl, et al., *Scientific World J.*, **2002**, *2*, 324-338; Chun, J., Hla, T., Spiegel, S., Moolenaar, W., Editors, *Lysophospholipid Receptors: Signaling and Biochemistry*, **2013**, Wiley; ISBN: 978-0-470-56905-4). The body of knowledge about the biology of LPA continues to grow as more and more cellular systems are tested for LPA responsiveness. For instance, it is now known that, in addition to stimulating cell growth and proliferation, LPAs promote cellular tension and cell-surface fibronectin binding, which are important events in wound repair and regeneration (Moolenaar et al., *BioEssays*, **2004**, *26*, 870-881). Recently, anti-apoptotic activity has also been ascribed to LPA, and it has recently been reported that PPAR γ is a receptor/target for LPA (Simon et al., *J. Biol. Chem.*, **2005**, *280*, 14656-14662).

Fibrosis is the result of an uncontrolled tissue healing process leading to excessive accumulation and insufficient resorption of extracellular matrix (ECM) which ultimately results in end-organ failure (Rockey, D. C., et al., *New Engl. J. Med.*, **2015**, *372*, 1138-1149). The LPA₁ receptor has been reported to be over-expressed in idiopathic pulmonary fibrosis (IPF) patients. LPA₁ receptor knockout mice were protected from bleomycin-induced lung fibrosis (Tager et al., *Nature Med.*, **2008**, *14*, 45-54). The LPA₁ antagonist BMS-986020 was shown to significantly reduce the rate of FVC (forced vital capacity) decline in a 26-week clinical trial in IPF patients (Palmer et al., *Chest*, **2018**, *154*, 1061-

1069). LPA pathway inhibitors (e.g. an LPA₁ antagonist) were shown to be chemopreventive anti-fibrotic agents in the treatment of hepatocellular carcinoma in a rat model (Nakagawa et al., *Cancer Cell*, **2016**, 30, 879-890).

Thus, antagonizing the LPA₁ receptor may be useful for the treatment of fibrosis such as pulmonary fibrosis, hepatic fibrosis, renal fibrosis, arterial fibrosis and systemic sclerosis, and thus the diseases that result from fibrosis (pulmonary fibrosis-Idiopathic Pulmonary Fibrosis [IPF], hepatic fibrosis-Non-alcoholic Steatohepatitis [NASH], renal fibrosis-diabetic nephropathy, systemic sclerosis-scleroderma, etc.).

10 SUMMARY OF THE INVENTION

The present invention provides novel substituted triazole compounds including stereoisomers, tautomers, and pharmaceutically acceptable salts or solvates thereof, which are useful as antagonists against one or more of the lysophosphatidic acid (LPA) receptors, especially the LPA₁ receptor.

15 The present invention also provides processes and intermediates for making the compounds of the present invention.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts or solvates thereof.

20 The compounds of the invention may be used in the treatment of conditions in which LPA plays a role.

The compounds of the present invention may be used in therapy.

The compounds of the present invention may be used for the manufacture of a medicament for the treatment of a condition in which inhibition of the physiological activity of LPA is useful, such as diseases in which an LPA receptor participates, is involved in the etiology or pathology of the disease, or is otherwise associated with at least one symptom of the disease.

30 In another aspect, the present invention is directed to a method of treating fibrosis of organs (liver, kidney, lung, heart and the like as well as skin), liver diseases (acute hepatitis, chronic hepatitis, liver fibrosis, liver cirrhosis, portal hypertension, regenerative failure, non-alcoholic steatohepatitis (NASH), liver hypofunction, hepatic blood flow

disorder, and the like), cell proliferative disease [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, and the like], inflammatory disease (psoriasis, nephropathy, pneumonia and the like),
5 gastrointestinal tract disease (irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), abnormal pancreatic secretion, and the like), renal disease, urinary tract-associated disease (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 (obstruction of lower urinary
10 tract, and the like), inflammatory disease of lower urinary tract, dysuria, frequent urination, and the like), pancreas disease, abnormal angiogenesis-associated disease (arterial obstruction and the like), scleroderma, brain-associated disease (cerebral infarction, cerebral hemorrhage, and the like), neuropathic pain, peripheral neuropathy, and the like, ocular disease (age-related macular degeneration (AMD), diabetic
15 retinopathy, proliferative vitreoretinopathy (PVR), cicatricial pemphigoid, glaucoma filtration surgery scarring, and the like).

In another aspect, the present invention is directed to a method of treating diseases, disorders, or conditions in which activation of at least one LPA receptor by LPA contributes to the symptomology or progression of the disease, disorder or condition.
20 These diseases, disorders, or conditions may arise from one or more of a genetic, iatrogenic, immunological, infectious, metabolic, oncological, toxic, surgical, and/or traumatic etiology.

In another aspect, the present invention is directed to a method of treating renal fibrosis, pulmonary fibrosis, hepatic fibrosis, arterial fibrosis and systemic sclerosis
25 comprising administering to a patient in need of such treatment a compound of the present invention as described above.

In one aspect, the present invention provides methods, compounds, pharmaceutical compositions, and medicaments described herein that comprise antagonists of LPA receptors, especially antagonists of LPA₁.

30 The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, preferably one to two other agent(s).

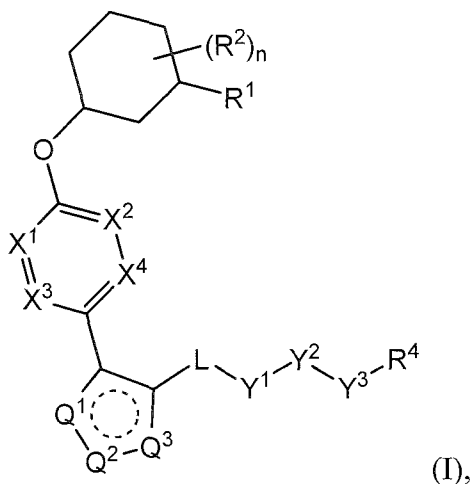
These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION OF THE INVENTION

5

I. COMPOUNDS OF THE INVENTION

In one aspect, the present invention provides, *inter alia*, compounds of Formula (I):



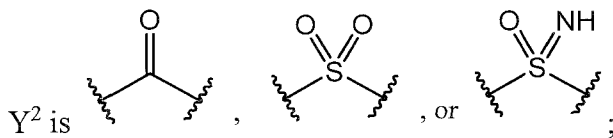
10 or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein

X^1 , X^2 , X^3 , and X^4 are each independently CR^6 or N; provided that no more than two of X^1 , X^2 , X^3 , or X^4 are N;

Q^2 is N or NR^{5a} ;

15 one of Q^1 and Q^3 is CR^5 , and the other is N or NR^{5a} ; and the dashed circle denotes optional bonds forming an aromatic ring;

Y^1 is O or NR^3 ;



Y^3 is O or NR^{4a} ; provided that (1) Y^1 and Y^3 are not both O, and (2) when Y^2 is

20 $C(O)$, Y^1 is not O;

L is a covalent bond or C_{1-4} alkylene substituted with 0 to 4 R^7 ;

R^1 is $(-CH_2)_aR^9$;

a is an integer of 0 or 1;

R² is each independently halo, cyano, hydroxyl, amino, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkoxyalkyl, haloalkoxyalkyl, or haloalkoxy;

n is an integer of 0, 1, or 2;

5 R³ and R^{4a} are independently hydrogen, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R⁴ is C₁₋₁₀ alkyl, C₁₋₁₀ deuterated alkyl (fully or partially deuterated), C₁₋₁₀ haloalkyl, C₁₋₁₀ alkenyl, C₃₋₈ cycloalkyl, 6 to 10-membered aryl, 3 to 8-membered heterocyclyl, -(C₁₋₆ alkylene)-(C₃₋₈ cycloalkyl), -(C₁₋₆ alkylene)-(6 to 10-membered aryl),
 10 -(C₁₋₆ alkylene)-(3 to 8-membered heterocyclyl), or -(C₁₋₆ alkylene)-(5 to 6-membered heteroaryl); wherein each of the alkyl, alkylene, alkenyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, by itself or as part of other moiety, is independently substituted with 0 to 3 R⁸; or alternatively, R³ and R⁴, taken together with the N and O atoms which they are attached, form a 4 to 9-membered heterocyclic ring moiety which is substituted with 0 to
 15 3 R⁸; or alternatively, (R³ and R^{5a}) or (R³ and R⁵), taken together with the atoms to which they are attached to, form a 5 to 8-membered heterocyclic ring moiety which is substituted with 0 to 3 R⁸;

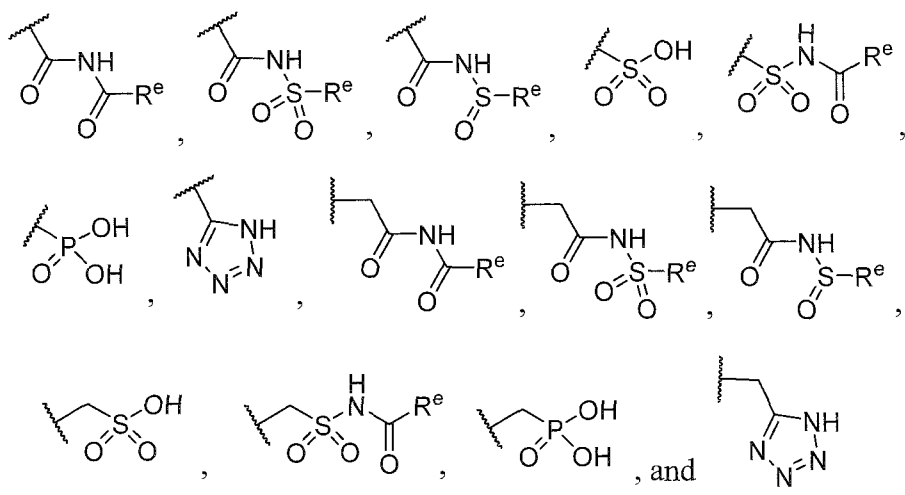
R^{5a} is hydrogen, C₁₋₆ alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

20 R⁵ and R⁶ are each independently hydrogen, halo, cyano, hydroxyl, amino, C₁₋₆ alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R⁷ is halo, oxo, cyano, hydroxyl, amino, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl,
 25 haloalkoxyalkyl, alkoxy, or haloalkoxy;

R⁸ are each independently deuterium, halo, hydroxyl, amino, cyano, C₁₋₆ alkyl, C₁₋₆ deuterated alkyl (fully or partially deuterated), C₂₋₆ alkenyl, C₂₋₆ alkynyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5 to 6-membered heteroaryl; or alternatively, two R⁸, taken together with the
 30 atom(s) to which they are attached, form a 3 to 6-membered carbocyclic ring or a 3 to 6-membered heterocyclic ring each of which is independently substituted with 0 to 3 R¹²;

R⁹ is selected from -CN, -C(O)OR¹⁰, -C(O)NR^{11a}R^{11b},



R^e is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, or haloalkoxyalkyl;

R¹⁰ is hydrogen or C₁₋₁₀ alkyl;

- 5 R^{11a} and R^{11b} are each independently hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; and

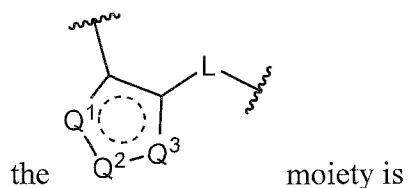
- R¹² is halo, cyano, hydroxyl, amino, C₁₋₆ alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5
10 to 6-membered heteroaryl.

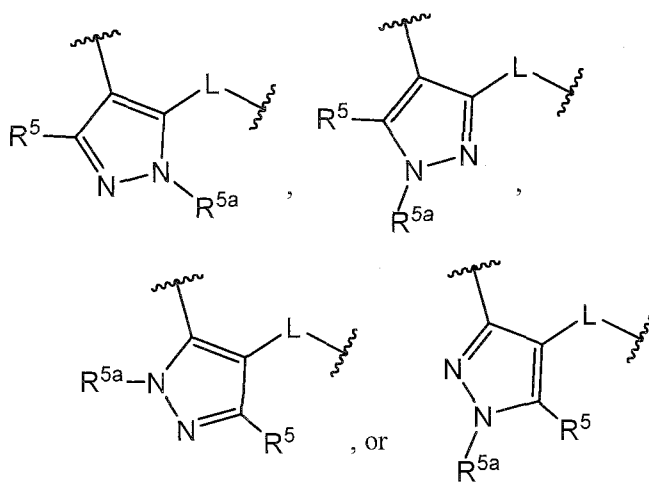
In one embodiment of Formula (I), X¹ is CR⁶, where R⁶ is hydrogen or C₁₋₄ alkyl, e.g., methyl.

In any one of the preceding embodiments of Formula (I), two R⁸, as substituents on cycloalkyl or heterocyclyl, together form a bridge moiety.

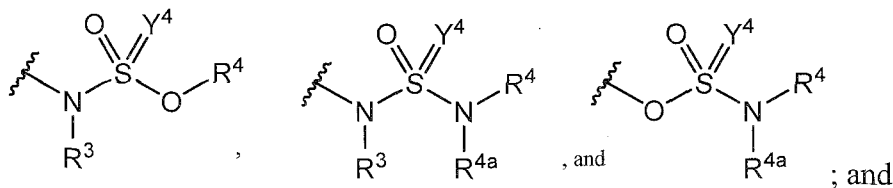
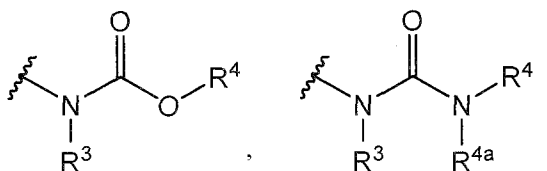
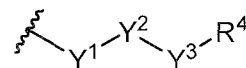
- 15 In any one of the preceding embodiments of Formula (I), L is methylene.

In any one of the preceding embodiments of Formula (I),





In any one of the preceding embodiments of Formula (I), the moiety is selected from



5 Y^4 is O or NH.

In any one of the preceding embodiments of Formula (I), n is 0.

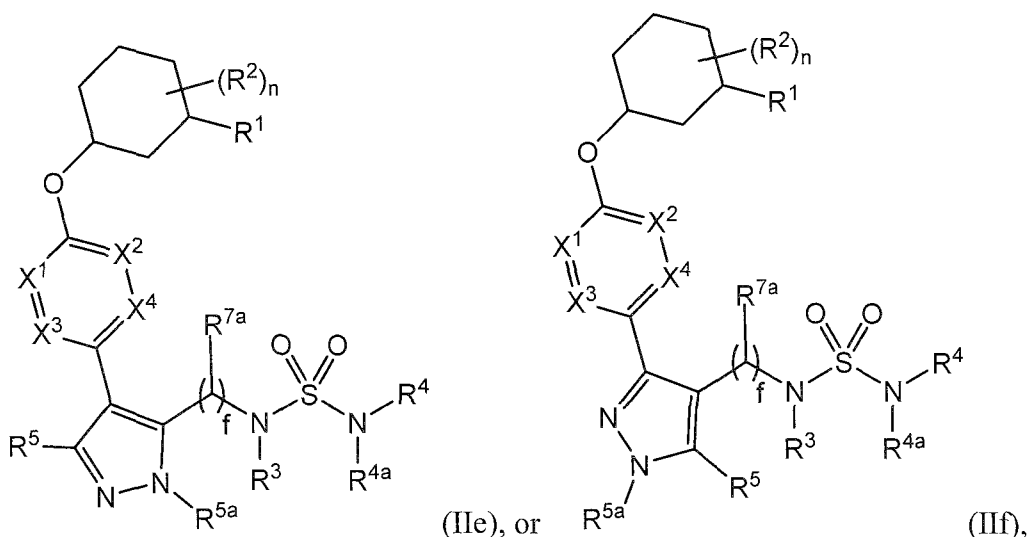
In any one of the preceding embodiments of Formula (I), R^1 is CO_2H .

In any one of the preceding embodiments of Formula (I), R^5 is hydrogen.

10 In any one of the preceding embodiments of Formula (I), R^{5a} is C_{1-4} alkyl. In one embodiment, R^{5a} is methyl.

In any one of the preceding embodiments of Formula (I), R^4 is C_{1-10} alkyl, C_{1-10} haloalkyl, C_{3-6} cycloalkyl, $-(C_{1-4}$ alkylene)- $(C_{3-6}$ cycloalkyl), or benzyl; wherein the alkyl, alkylene, cycloalkyl, and benzyl are each independently substituted with 0 to 3 R^8 ; and R^8 is each independently halo, hydroxyl, amino, cyano, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, or phenyl.

15 The alkyl and alkylene are each independently straight-chain or branched; and the



each R^{7a} is independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

5 f is an integer of 1, 2, or 3;

n is 0 or 1;

R^3 and R^{4a} are each independently hydrogen or C_{1-4} alkyl;

R^5 and R^{5a} are each independently hydrogen or C_{1-4} alkyl; or alternatively, (R^3 and R^{5a}) or (R^3 and R^5), taken together with the atoms to which they are attached to, form a 6

10 to 8-membered heterocyclic ring moiety; and

R^1 , R^2 , n , R^4 , R^5 , R^{5a} , X^1 , X^2 , X^3 , and X^4 are the same as defined above.

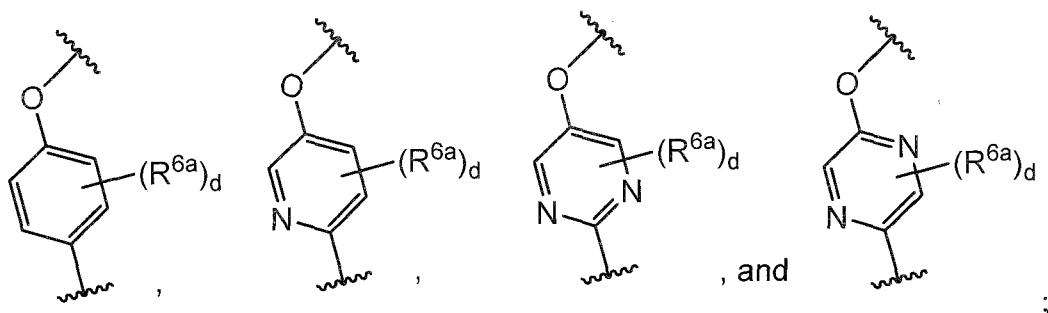
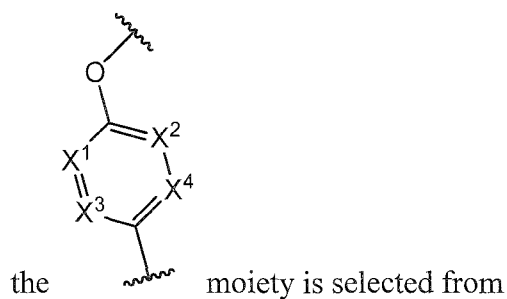
In one embodiment of Formula (IIa) or (IIb), R^1 is CO_2H .

In any one of the preceding embodiments of Formula (IIa) or (IIb), X^1 is CR^6 , where R^6 is hydrogen or C_{1-4} alkyl. In one embodiment, X^1 is CH or CCH_3 .

15 In any one of the preceding embodiments of Formula (IIa) or (IIb), X^3 is N.

In any one of the preceding embodiments of Formula (IIa) or (IIb), X^1 , X^2 , X^3 , and X^4 are CR^6 , where each R^6 is independently hydrogen or C_{1-4} alkyl. In one embodiment, X^1 , X^2 , X^3 , and X^4 are CH.

In any one of the preceding embodiments of Formula (IIa) or (IIb),

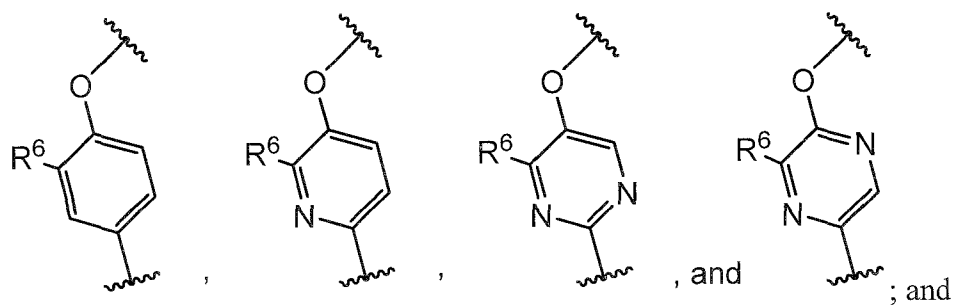
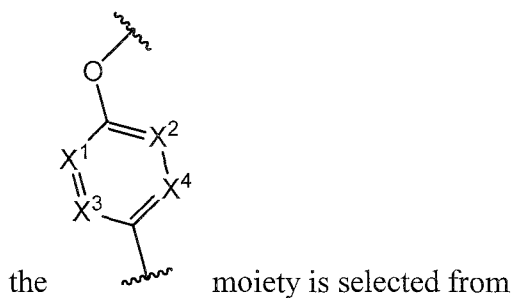


R^{6a} is each independently halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or

5 haloalkoxy; and

d is an integer of 0, 1, or 2.

In any one of the preceding embodiments of Formula (IIa) or (IIb),

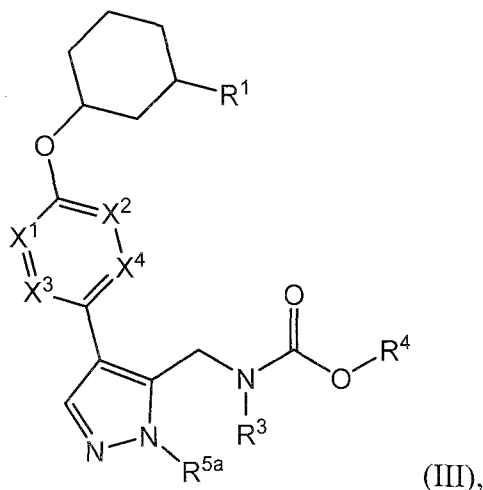


10

R^6 is each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy.

In any one of the preceding embodiments of Formula (IIa) or (IIb), L is methylene, or f is 1. In one embodiment, R^{7a} is hydrogen.

In one embodiment of the present invention, the compound is represented by Formula (III):

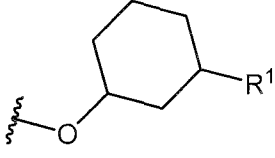


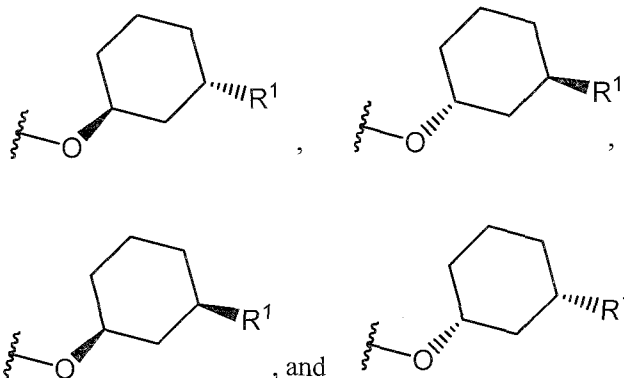
R³ is methyl;

R^{5a} is methyl; or alternatively, R³ and R^{5a}, taken together with the atoms to which they are attached to, form a 6 or 7-membered heterocyclic ring moiety; and

R¹, R⁴, X¹, X², X³, and X⁴ are the same as defined above.

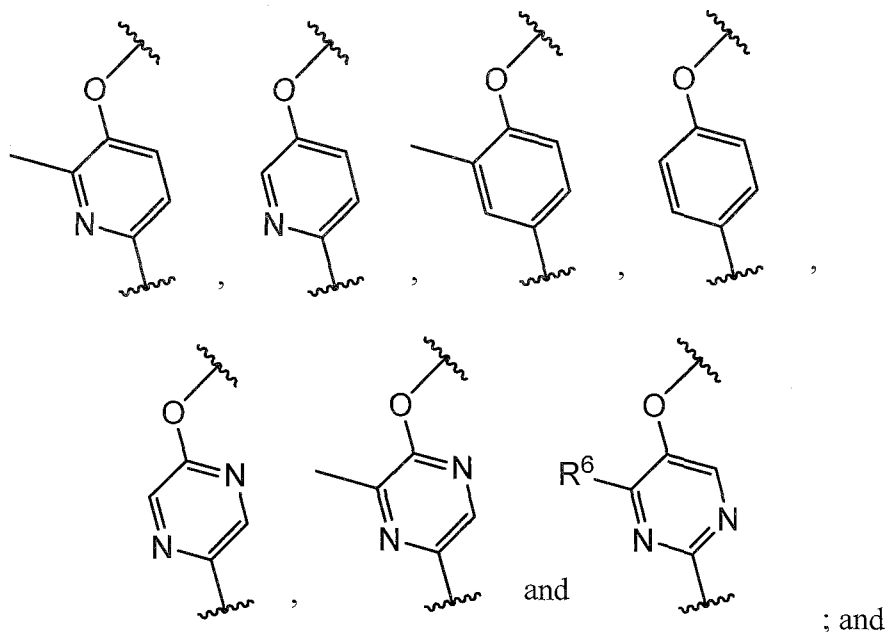
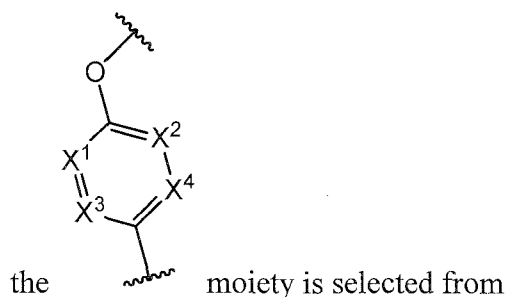
10

In one embodiment of Formula (III), the  moiety is selected from



In any one of the preceding embodiments of Formula (III), R¹ is CO₂H.

In any one of the preceding embodiments of Formula (III),



R^6 is hydrogen, CH_3 , or CH_2CH_3 .

In any one of the preceding embodiments of Formula (III), R^4 is C_{3-10} alkyl, C_{3-10} haloalkyl, C_{3-6} cycloalkyl, $-(C_{1-4}$ alkylene)-(C_{1-3} alkoxy), $-(C_{1-4}$ alkylene)-(C_{3-6} cycloalkyl), or $-(C_{1-4}$ alkylene)-phenyl; wherein the alkyl, alkylene, cycloalkyl, and phenyl are each independently substituted with 0 to 3 R^8 ; and R^8 is each independently halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy. The alkyl and alkylene are each independently straight-chain or branched; and the methylene and the phenyl moieties of the benzyl are each independently substituted with 0 to 3 R^8 .

In any one of the preceding embodiments of Formula (III), R^4 is C_{3-10} alkyl, C_{3-10} haloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, $-(CHR^{8a})_{1-2}$ -cyclopropyl, $-(CHR^{8a})$ -cyclobutyl, or $-CH_2$ -phenyl; wherein the cyclopropyl and cyclobutyl are each substituted with 0 to 2 R^8 , and the phenyl is substituted with 0 to 2 halo selected from fluoro and chloro; R^8 is each independently methyl, ethyl, propyl, or cyclopropyl; and R^{8a} is each independently hydrogen or methyl.

In one embodiment of the present invention, the compound is selected from any one of the Examples as described in the specification, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment of the present invention, the compound is selected from
5 Examples 1 to 44 as described in the specification, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the compounds of the present invention have hLPA₁ IC₅₀ values ≤ 5000 nM, using the LPA₁ functional antagonist assay; in another embodiment, the compounds of the present invention have hLPA₁ IC₅₀ values ≤ 1000 nM; in another
10 embodiment, the compounds of the present invention have hLPA₁ IC₅₀ values ≤ 500 nM; in another embodiment, the compounds of the present invention have hLPA₁ IC₅₀ values ≤ 200 nM; in another embodiment, the compounds of the present invention have hLPA₁ IC₅₀ values ≤ 100 nM; in another embodiment, the compounds of the present invention have hLPA₁ IC₅₀ values ≤ 50 nM.

15

II. OTHER EMBODIMENTS OF THE INVENTION

In some embodiments, the compound of Formulas (I), or a pharmaceutically acceptable salt or solvate thereof, is an antagonist of at least one LPA receptor. In some
20 embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is an antagonist of LPA₁. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is an antagonist of LPA₂. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is an antagonist of LPA₃.

In some embodiments, presented herein are compounds selected from active
25 metabolites, tautomers, pharmaceutically acceptable salts or solvates of a compound of Formula (I).

In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

30 In another embodiment, the present invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically

effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a process for making a compound of the present invention.

5 In another embodiment, the present invention provides an intermediate for making a compound of the present invention.

In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s).

10 In another embodiment, the present invention provides a method for the treatment of a condition associated with LPA receptor mediated fibrosis, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof. As used herein, the term "patient" encompasses all mammalian species.

15 In another embodiment, the present invention provides a method of treating a disease, disorder, or condition associated with dysregulation of lysophosphatidic acid receptor 1 (LPA₁) in a patient in need thereof, comprising administering a therapeutically effective amount of a compound of the present invention, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, to the patient. In one
20 embodiment of the method, the disease, disorder, or condition is related to pathological fibrosis, transplant rejection, cancer, osteoporosis, or inflammatory disorders. In one embodiment of the method, the pathological fibrosis is pulmonary, liver, renal, cardiac, dermal, ocular, or pancreatic fibrosis. In one embodiment of the method, the disease, disorder, or condition is idiopathic pulmonary fibrosis (IPF), non-alcoholic steatohepatitis
25 (NASH), non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, diabetic kidney disease, and systemic sclerosis. In one embodiment of the method, the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin,
30 spleen, small intestine, large intestine, stomach, testicle, or thyroid.

In another embodiment, the present invention provides a method of treating fibrosis in a mammal comprising administering a therapeutically effective amount of a

compound of the present invention, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, to the mammal in need thereof. In one embodiment of the method, the fibrosis is idiopathic pulmonary fibrosis (IPF), nonalcoholic steatohepatitis (NASH), chronic kidney disease, diabetic kidney disease, and systemic sclerosis.

In another embodiment, the present invention provides a method of treating lung fibrosis (idiopathic pulmonary fibrosis), asthma, chronic obstructive pulmonary disease (COPD), renal fibrosis, acute kidney injury, chronic kidney disease, liver fibrosis (non-alcoholic steatohepatitis), skin fibrosis, fibrosis of the gut, breast cancer, pancreatic cancer, ovarian cancer, prostate cancer, glioblastoma, bone cancer, colon cancer, bowel cancer, head and neck cancer, melanoma, multiple myeloma, chronic lymphocytic leukemia, cancer pain, tumor metastasis, transplant organ rejection, scleroderma, ocular fibrosis, age related macular degeneration (AMD), diabetic retinopathy, collagen vascular disease, atherosclerosis, Raynaud's phenomenon, or neuropathic pain in a mammal comprising administering a therapeutically effective amount of a compound of the present invention, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, to the mammal in need thereof.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting the disease-state, *i.e.*, arresting its development; and/or (b) relieving the disease-state, *i.e.*, causing regression of the disease state. As used herein, "treating" or "treatment" also include the protective treatment of a disease state to reduce and/or minimize the risk and/or reduction in the risk of recurrence of a disease state by administering to a patient a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof. Patients may be selected for such protective therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. For protective treatment, conditions of the clinical disease state may or may not be presented yet. The protective treatment can be divided into (a) primary prophylaxis and (b) secondary prophylaxis. Primary prophylaxis is defined as treatment to reduce or minimize the risk of a disease state in a patient that has not yet presented with a clinical disease state, whereas

secondary prophylaxis is defined as minimizing or reducing the risk of a recurrence or second occurrence of the same or similar clinical disease state.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also to be understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. *Cis-* and *trans-* (or *E-* and *Z-*) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual

isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers and diastereomers are examples of stereoisomers. The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superimposable. The term "diastereomer" refers to stereoisomers that are not mirror images. The term "racemate" or "racemic mixture" refers to a composition composed of equimolar quantities of two enantiomeric species, wherein the composition is devoid of optical activity.

The symbols "R" and "S" represent the configuration of substituents around a chiral carbon atom(s). The isomeric descriptors "R" and "S" are used as described herein for indicating atom configuration(s) relative to a core molecule and are intended to be used as defined in the literature (IUPAC Recommendations 1996, *Pure and Applied Chemistry*, 68:2193-2222 (1996)).

The term "chiral" refers to the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image. The term "homochiral" refers to a state of enantiomeric purity. The term "optical activity" refers to the degree to which a homochiral molecule or nonracemic mixture of chiral molecules rotates a plane of polarized light.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. While "alkyl" denotes a monovalent saturated aliphatic radical (such as ethyl), "alkylene" denotes a bivalent saturated aliphatic radical (such as ethylene). For example, "C₁ to C₁₀ alkyl" or "C₁₋₁₀ alkyl" is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkyl groups. "C₁ to C₁₀ alkylene" or "C₁₋₁₀ alkylene", is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkylene groups. Additionally, for example, "C₁ to C₆ alkyl" or "C₁₋₆ alkyl" denotes alkyl having 1 to 6 carbon atoms; and "C₁ to C₆ alkylene" or "C₁₋₆ alkylene" denotes alkylene having 1 to 6 carbon atoms; and "C₁ to C₄ alkyl" or "C₁₋₄ alkyl" denotes alkyl having 1 to 4

carbon atoms; and "C₁ to C₄ alkylene" or "C₁₋₄ alkylene" denotes alkylene having 1 to 4 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, *n*-propyl and isopropyl), butyl (*e.g.*,
5 *n*-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, *n*-pentyl, isopentyl, neopentyl). When "C₀ alkyl" or "C₀ alkylene" is used, it is intended to denote a direct bond. Furthermore, the term "alkyl", by itself or as part of another group, such as alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkoxyalkyl, haloalkoxyalkyl, and haloalkoxy, can be an alkyl having 1 to 4 carbon atoms, or 1 to 6 carbon atoms, or 1 to 10 carbon atoms.

10 "Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (*e.g.*, O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (*e.g.*, -OCH₃, etc.), an alkylamino (*e.g.*, -NHCH₃, -N(CH₃)₂, etc.), or a thioalkyl group (*e.g.*, -SCH₃). If a non-
15 terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (*e.g.*, O, N, or S) and the resulting heteroalkyl groups are, respectively, an alkyl ether (*e.g.*, -CH₂CH₂-O-CH₃, etc.), an alkylaminoalkyl (*e.g.*, -CH₂NHCH₃, -CH₂N(CH₃)₂, etc.), or a thioalkyl ether (*e.g.*, -CH₂-S-CH₃). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (*e.g.*, O, N, or S), the resulting
20 heteroalkyl groups are, respectively, a hydroxyalkyl group (*e.g.*, -CH₂CH₂-OH), an aminoalkyl group (*e.g.*, -CH₂NH₂), or an alkyl thiol group (*e.g.*, -CH₂CH₂-SH). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C₁-C₆ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

25 "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C₂ to C₆ alkenyl" or "C₂₋₆ alkenyl" (or alkenylene), is intended to include C₂, C₃, C₄, C₅, and C₆ alkenyl groups. Examples of alkenyl include,
30 but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C₂ to C₆ alkynyl" or "C₂₋₆ alkynyl" (or alkynylene), is intended to include C₂, C₃, C₄, C₅, and C₆ alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

As used herein, "arylalkyl" (a.k.a. aralkyl), "heteroarylalkyl" "carbocyclalkyl" or "heterocyclalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon atom, is replaced with an aryl, heteroaryl, carbocycl, or heterocycl radical, respectively. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl, heteroarylalkyl, carbocyclalkyl, or heterocyclalkyl group can comprise 4 to 20 carbon atoms and 0 to 5 heteroatoms, *e.g.*, the alkyl moiety may contain 1 to 6 carbon atoms.

The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group, wherein said phenyl group may optionally be substituted with 1 to 5 groups, preferably 1 to 3 groups, OH, OCH₃, Cl, F, Br, I, CN, NO₂, NH₂, N(CH₃)H, N(CH₃)₂, CF₃, OCF₃, C(=O)CH₃, SCH₃, S(=O)CH₃, S(=O)₂CH₃, CH₃, CH₂CH₃, CO₂H, and CO₂CH₃. "Benzyl" can also be represented by formula "Bn".

The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. "C₁ to C₆ alkoxy" or "C₁₋₆ alkoxy" (or alkyloxy), is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example, methyl-S- and ethyl-S-.

The term "alkanoyl" or "alkylcarbonyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group. For example, alkylcarbonyl may be represented by alkyl-C(O)-. "C₁ to C₆ alkylcarbonyl" (or alkylcarbonyl), is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ alkyl-C(O)- groups.

The term "alkylsulfonyl" or "sulfonamide" as used herein alone or as part of another group refers to alkyl or amino linked to a sulfonyl group. For example, alkylsulfonyl may be represented by -S(O)₂R', while sulfonamide may be represented by

-S(O)₂NR^cR^d. R' is C₁ to C₆ alkyl; and R^c and R^d are the same as defined below for "amino".

The term "carbamate" as used herein alone or as part of another group refers to oxygen linked to an amido group. For example, carbamate may be represented by
 5 N(R^cR^d)-C(O)-O-, and R^c and R^d are the same as defined below for "amino".

The term "amido" as used herein alone or as part of another group refers to amino linked to a carbonyl group. For example, amido may be represented by N(R^cR^d)-C(O)-, and R^c and R^d are the same as defined below for "amino".

The term "amino" is defined as -NR^{c1}R^{c2}, wherein R^{c1} and R^{c2} are independently
 10 H or C₁₋₆ alkyl; or alternatively, R^{c1} and R^{c2}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more group selected from halo, cyano, hydroxyl, amino, oxo, C₁₋₆ alkyl, alkoxy, and aminoalkyl. When R^{c1} or R^{c2} (or both of them) is C₁₋₆ alkyl, the amino group can also be referred to as alkylamino. Examples of alkylamino group include, without
 15 limitation, methylamino, ethylamino, propylamino, isopropylamino and the like. In one embodiment, amino is -NH₂.

The term "aminoalkyl" refers to an alkyl group on which one of the hydrogen atoms is replaced by an amino group. For example, aminoalkyl may be represented by N(R^{c1}R^{c2})-alkylene-. "C₁ to C₆" or "C₁₋₆" aminoalkyl" (or aminoalkyl), is intended to
 20 include C₁, C₂, C₃, C₄, C₅, and C₆ aminoalkyl groups.

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine, with chlorine or fluorine being preferred.

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted
 25 with one or more halogens. "C₁ to C₆ haloalkyl" or "C₁₋₆ haloalkyl" (or haloalkyl), is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ haloalkyl groups. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include
 30 "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms. The term "polyhaloalkyl" as used herein refers to an

"alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as polyfluoroalkyl, for example, CF_3CH_2 , CF_3 or $\text{CF}_3\text{CF}_2\text{CH}_2$.

"Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C₁ to C₆ haloalkoxy" or "C₁₋₆ haloalkoxy", is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluoroethoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-. The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as polyfluoroalkoxy, for example, $\text{CF}_3\text{CH}_2\text{O}$, CF_3O or $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}$.

"Hydroxyalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more hydroxyl (OH). "C₁ to C₆ hydroxyalkyl" (or hydroxyalkyl), is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ hydroxyalkyl groups.

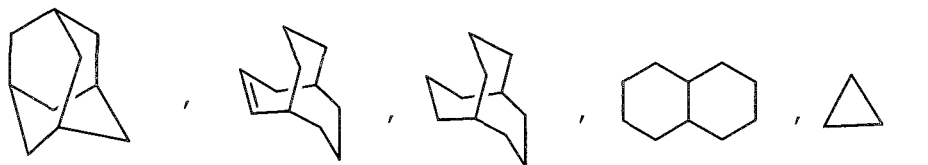
The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. "C₃ to C₈ cycloalkyl" or "C₃₋₈ cycloalkyl" is intended to include C₃, C₄, C₅, C₆, C₇, and C₈ cycloalkyl groups, including monocyclic, bicyclic, and polycyclic rings. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl and spiro and bridged cycloalkyl groups are included in the definition of "cycloalkyl".

The term "cycloheteroalkyl" refers to cyclized heteroalkyl groups, including mono-, bi- or poly-cyclic ring systems. "C₃ to C₇ cycloheteroalkyl" or "C₃₋₇ cycloheteroalkyl" is intended to include C₃, C₄, C₅, C₆, and C₇ cycloheteroalkyl groups. Example cycloheteroalkyl groups include, but are not limited to, oxetanyl, tetrahydrofuranlyl, tetrahydropyranyl, azetidinylyl, pyrrolidinyl, piperidinyl, morpholinyl, and piperazinyl. Branched cycloheteroalkyl groups, such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl,

pyrimidylmethyl, and pyrazinylmethyl, are included in the definition of "cycloheteroalkyl".

As used herein, "carbocycle", "carbocyclyl" or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and indanyl. When the term "carbocyclyl" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

Furthermore, the term "carbocyclyl", including "cycloalkyl" and "cycloalkenyl", as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons or 3 to 6 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido,

alkanoylamino, oxo, acyl, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio and/or any of the alkyl substituents.

As used herein, the term "bicyclic carbocyclyl" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

As used herein, the term "aryl", as employed herein alone or as part of another group, refers to monocyclic or polycyclic (including bicyclic and tricyclic) aromatic hydrocarbons, including, for example, phenyl, naphthyl, anthracenyl, and phenanthryl. Aryl moieties are well known and described, for example, in Lewis, R.J., ed., *Hawley's Condensed Chemical Dictionary*, 13th Edition, John Wiley & Sons, Inc., New York (1997). In one embodiment, the term "aryl" denotes monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl). For example, "C₆ or C₁₀ aryl" or "C₆₋₁₀ aryl" refers to phenyl and naphthyl. Unless otherwise specified, "aryl", "C₆ or C₁₀ aryl", "C₆₋₁₀ aryl", or "aromatic residue" may be unsubstituted or substituted with 1 to 5 groups, preferably 1 to 3 groups, selected from -OH, -OCH₃, -Cl, -F, -Br, -I, -CN, -NO₂, -NH₂, -N(CH₃)H, -N(CH₃)₂, -CF₃, -OCF₃, -C(O)CH₃, -SCH₃, -S(O)CH₃, -S(O)₂CH₃, -CH₃, -CH₂CH₃, -CO₂H, and -CO₂CH₃.

The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group, wherein said phenyl group may optionally be substituted with 1 to 5 groups, preferably 1 to 3 groups, OH, OCH₃, Cl, F, Br, I, CN, NO₂, NH₂, N(CH₃)H, N(CH₃)₂, CF₃, OCF₃, C(=O)CH₃, SCH₃, S(=O)CH₃, S(=O)₂CH₃, CH₃, CH₂CH₃, CO₂H, and CO₂CH₃.

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic (including bicyclic and tricyclic)

heterocyclic ring that is saturated, or partially unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a carbocyclic or an aryl (e.g., benzene) ring. That is, the term "heterocycle",
5 "heterocyclyl", or "heterocyclic group" includes non-aromatic ring systems, such as heterocycloalkyl and heterocycloalkenyl. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and S(O)_p, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom
10 or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the
15 heterocycle is not more than 1. Examples of heterocyclyl include, without limitation, azetidiny, piperaziny, piperidiny, piperidonyl, piperonyl, pyranyl, morpholinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, morpholinyl, dihydrofuro[2,3-*b*]tetrahydrofuran.

As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is
20 intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or
25 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic
30 group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is

preferred that the total number of S and O atoms in the heterocycle is not more than 1. Examples of a bicyclic heterocyclic group are, but not limited to, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxaliny, and 1,2,3,4-tetrahydro-quinazoliny.

Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

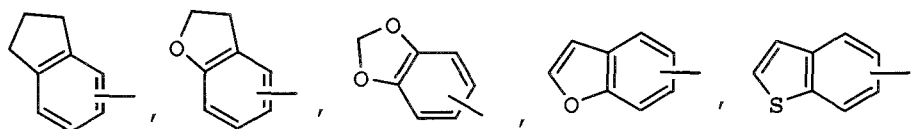
As used herein, the term "heteroaryl" is intended to mean stable monocyclic and polycyclic (including bicyclic and tricyclic) aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and S(O)_p, wherein p is 0, 1 or 2).

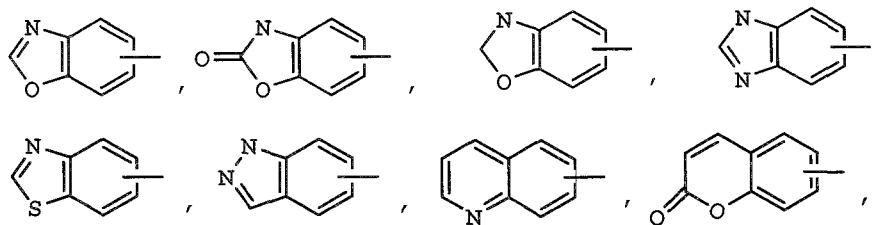
Examples of heteroaryl also include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4*H*-carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2*H*,6*H*-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidiny, imidazoliny, imidazolyl, 1*H*-indazolyl, imidazolopyridiny, indolenyl, indolinyl, indoliziny, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isothiazolopyridiny, isoxazolyl, isoxazolopyridiny, methylenedioxyphenyl, naphthyridiny,

octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,
 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl,
 oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl,
 phenazinyl, phenothiazinyl, phenoxathianyl, phenoxazinyl, phthalazinyl, pteridinyl,
 5 purinyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl,
 pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl,
 pyrrolinyl, 2-pyrrolidonyl, 2H-pyrrolyl, pyrrolyl, quinazoliny, quinolinyl,
 4*H*-quinoliziny, quinoxaliny, quinuclidinyl, tetrazolyl, tetrahydrofuranyl,
 tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl,
 10 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl,
 thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl,
 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

Examples of 5- to 10-membered heteroaryl include, but are not limited to,
 pyridinyl, furanyl, thienyl, pyrazolyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl,
 15 isoxazolyl, oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl,
 triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl,
 benzotetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazoliny,
 benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl,
 isoxazolopyridinyl, quinazoliny, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl,
 20 oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl. Examples of 5- to
 6-membered heteroaryl include, but are not limited to, pyridinyl, furanyl, thienyl,
 pyrrolyl, pyrazolyl, pyrazinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
 oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and
 triazolyl. In some embodiments, the heteroaryl are selected from benzthiazolyl,
 25 imidazolpyridinyl, pyrrolopyridinyl, quinolinyl, and indolyl.


Unless otherwise indicated, "carbocyclyl" or "heterocyclyl" includes one to three
 additional rings fused to the carbocyclic ring or the heterocyclic ring (such as aryl,
 cycloalkyl, heteroaryl or cycloheteroalkyl rings), for example,



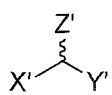


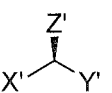
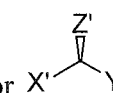
and may be optionally substituted through available carbon or nitrogen atoms (as applicable) with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino and arylsulfonaminocarbonyl and/or any of the alkyl substituents set out herein.

When any of the terms alkyl, alkenyl, alkynyl, cycloalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are used as part of another group, the number of carbon atoms and ring members are the same as those defined in the terms by themselves. For example, alkoxy, haloalkoxy, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, haloalkoxy, alkoxyalkoxy, haloalkylamino, alkoxyalkylamino, haloalkoxyalkylamino, alkylthio, and the like each independently contains the number of carbon atoms which are the same as defined for the term "alkyl", such as 1 to 4 carbon atoms, 1 to 6 carbon atoms, 1 to 10 carbon atoms, etc. Similarly, cycloalkoxy, heterocyclioxy, cycloalkylamino, heterocyclylamino, aralkylamino, arylamino, aryloxy, aralkyloxy, heteroaryloxy, heteroarylalkyloxy, and the like each independently contains ring members which are the same as defined for the terms "cycloalkyl", "heterocyclyl", "aryl", and "heteroaryl", such as 3 to 6-membered, 4 to 7-membered, 6 to 10-membered, 5 to 10-membered, 5 or 6-membered, etc.

In accordance with a convention used in the art, a bond pointing to a bold line, such as  as used in structural formulas herein, depicts the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

In accordance with a convention used in the art, a wavy or squiggly bond in a

structural formula, such as , is used to depict a stereogenic center of the carbon atom to which X', Y', and Z' are attached and is intended to represent both enantiomers in a single figure. That is, a structural formula with such as wavy bond denotes each of

5 the enantiomers individually, such as  or , as well as a racemic mixture thereof. When a wavy or squiggly bond is attached to a double bond (such as C=C or C=N) moiety, it include *cis*- or *trans*- (or *E*- and *Z*-) geometric isomers or a mixture thereof.

10 It is understood herein that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term “pyridyl” means 2-, 3- or 4-pyridyl, the term “thienyl” means 2- or 3-thienyl, and so forth.

15 When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such

20 combinations result in stable compounds.

One skilled in the art will recognize that substituents and other moieties of the compounds of the present invention should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of the

25 present invention which have such stability are contemplated as falling within the scope of the present invention.

The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate. The term “metal ion” refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as

30 magnesium and calcium, as well as zinc and aluminum.

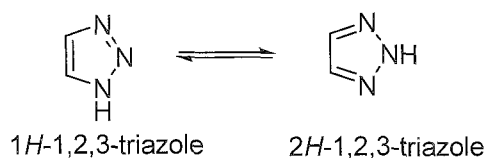
As referred to herein, the term "substituted" means that at least one hydrogen atom (attached to carbon atom or heteroatom) is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. When a substituent is oxo (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Oxo substituents are not present on aromatic moieties. When a ring system (*e.g.*, carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (*i.e.*, within) of the ring. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N). The term "substituted" in reference to alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, alkylene, aryl, arylalkyl, heteroaryl, heteroarylalkyl, carbocyclyl, and heterocyclyl, means alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, alkylene, aryl, arylalkyl, heteroaryl, heteroarylalkyl, carbocyclyl, and heterocyclyl, respectively, in which one or more hydrogen atoms, which are attached to either carbon or heteroatom, are each independently replaced with one or more non-hydrogen substituent(s).

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0, 1, 2, or 3 R groups, then said group be unsubstituted when it is substituted with 0 R group, or be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R.

Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, the term "tautomer" refers to each of two or more isomers of a compound that exist together in equilibrium, and are readily interchanged by migration of an atom or group within the molecule. For example, one skilled in the art would readily understand that a 1,2,3-triazole exists in two tautomeric forms as defined above:



Thus, this disclosure is intended to cover all possible tautomers even when a structure depicts only one of them.

The phrase "pharmaceutically acceptable" is employed herein to refer to those
 5 compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, and/or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The compounds of the present invention can be present as salts, which are also
 10 within the scope of this invention. Pharmaceutically acceptable salts are preferred. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. The pharmaceutically acceptable salts of the present invention can be
 15 synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*,
 20 18th Edition, Mack Publishing Company, Easton, PA (1990), the disclosure of which is hereby incorporated by reference.

If the compounds of the present invention have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong
 25 inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms, for example acetic acid, which are unsubstituted or substituted, for example, by halogen as chloroacetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic,
 30 tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine

or arginine), or benzoic acid, or with organic sulfonic acids, such as (C₁-C₄) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of the present invention having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tert-butyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of Formula (I) or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of Formula (I) which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate, nitrate or acetate.

Preferred salts of the compounds of Formula (I) which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

In addition, compounds of Formula (I) may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);
- b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", *A Textbook of Drug Design and Development*, pp. 113-191, Krosgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);
- c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);
- d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988); and
- e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984).

The compounds of the present invention contain a carboxy group which can form physiologically hydrolyzable esters that serve as prodrugs, i.e., "prodrug esters", by being hydrolyzed in the body to yield the compounds of the present invention *per se*. Examples of physiologically hydrolyzable esters of compounds of the present invention include C₁ to C₆ alkyl, C₁ to C₆ alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C₁₋₆ alkanoyloxy-C₁₋₆ alkyl (e.g., acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C₁ to C₆ alkoxy-carbonyloxy-C₁ to C₆ alkyl (e.g., methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art. The "prodrug esters" can be formed by reacting the carboxylic acid moiety of the compounds of the present invention with either alkyl or aryl alcohol, halide, or sulfonate employing procedures known to those skilled in the art. Such esters may be prepared by conventional techniques known in the art.

Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (1994); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, Academic Press, San Diego, CA (1999).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Deuterium has one proton and one neutron in its nucleus and that has twice the mass of ordinary hydrogen. Deuterium can be represented by symbols such as "²H" or "D". The term "deuterated" herein, by itself or used to modify a compound or group, refers to replacement of one or more hydrogen atom(s), which is attached to carbon(s), with a deuterium atom. Isotopes of carbon include ¹³C and ¹⁴C.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the

non-labeled reagent otherwise employed. Such compounds have a variety of potential uses, *e.g.*, as standards and reagents in determining the ability of a potential pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors *in vivo* or *in vitro*.

5 "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that compounds of the present invention do not contain a N-halo, S(O)₂H, or S(O)H group.

10 The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise
15 either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanulates, methanulates, and isopropanulates. Methods of solvation are generally known in the art.

20

ABBREVIATIONS

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar,
25 "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "RT" for retention time, "RBF" for round bottom flask, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "RCM" for ring-closing metathesis, "sat" or "sat'd" for saturated, "SFC" for supercritical fluid chromatography "MW" for molecular weight, "mp" for melting point, "ee" for
30 enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for

high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "¹H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "γ", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
Pr	propyl
<i>i</i> -Pr	isopropyl
Bu	butyl
<i>i</i> -Bu	isobutyl
<i>t</i> -Bu	<i>tert</i> -butyl
Ph	phenyl
Bn	benzyl
Boc or BOC	<i>tert</i> -butyloxycarbonyl
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
AcOH or HOAc	acetic acid
AlCl ₃	aluminum trichloride
AIBN	Azobis-isobutyronitrile
BBr ₃	boron tribromide
BCl ₃	boron trichloride
BEMP	2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BOP reagent	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Burgess reagent	1-methoxy-N-triethylammoniosulfonyl-methanimidate
CBz	carbobenzyloxy
DCM or CH ₂ Cl ₂	dichloromethane
CH ₃ CN or ACN	acetonitrile
CDCl ₃	deutero-chloroform

CHCl ₃	chloroform
mCPBA or m-CPBA	<i>meta</i> -chloroperbenzoic acid
Cs ₂ CO ₃	cesium carbonate
Cu(OAc) ₂	copper (II) acetate
Cy ₂ NMe	N-cyclohexyl-N-methylcyclohexanamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2 dichloroethane
DEA	diethylamine
Dess-Martin	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one
DIC or DIPCDI	diisopropylcarbodiimide
DIEA, DIPEA or	diisopropylethylamine
Hunig's base	
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
cDNA	complementary DNA
Dppp	(<i>R</i>)-(+)-1,2-bis(diphenylphosphino)propane
DuPhos	(+)-1,2-bis((2 <i>S</i> ,5 <i>S</i>)-2,5-diethylphospholano)benzene
EDC	<i>N</i> -(3-dimthylaminopropyl)- <i>N'</i> -ethylcarbodiimide
EDCI	<i>N</i> -(3-dimthylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
(<i>S,S</i>)-EtDuPhosRh(I)	(+)-1,2-bis((2 <i>S</i> ,5 <i>S</i>)-2,5-diethylphospholano)benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate
Et ₃ N or TEA	triethylamine
EtOAc	ethyl acetate
Et ₂ O	diethyl ether
EtOH	ethanol
GMF	glass microfiber filter
Grubbs II	(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium
HCl	hydrochloric acid

HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
Hex	hexane
HOBt or HOBT	1-hydroxybenzotriazole
H ₂ O ₂	hydrogen peroxide
IBX	2-iodoxybenzoic acid
H ₂ SO ₄	sulfuric acid
Jones reagent	CrO ₃ in aqueous H ₂ SO ₄ , 2 M solution
K ₂ CO ₃	potassium carbonate
K ₂ HPO ₄	potassium phosphate dibasic (potassium hydrogen phosphate)
KOAc	potassium acetate
K ₃ PO ₄	potassium phosphate tribasic
LAH	lithium aluminum hydride
LG	leaving group
LiOH	lithium hydroxide
MeOH	methanol
MgSO ₄	magnesium sulfate
MsOH or MSA	methylsulfonic acid/methanesulfonic acid
NaCl	sodium chloride
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
Na ₂ CO ₃	sodium carbonate
NaOH	sodium hydroxide
Na ₂ SO ₃	sodium sulfite
Na ₂ SO ₄	sodium sulfate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NH ₃	ammonia
NH ₄ Cl	ammonium chloride
NH ₄ OH	ammonium hydroxide
NH ₄ ⁺ HCO ₂ ⁻	ammonium formate

NMM	N-methylmorpholine
OTf	triflate or trifluoromethanesulfonate
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
Pd(OAc) ₂	palladium(II) acetate
Pd/C	palladium on carbon
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)
Ph ₃ PCl ₂	triphenylphosphine dichloride
PG	protecting group
POCl ₃	phosphorus oxychloride
PPTS	pyridinium p-toluenesulfonate
i-PrOH or IPA	isopropanol
PS	Polystyrene
RT or rt	room temperature
SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
SiO ₂	silica oxide
SnCl ₂	tin(II) chloride
TBAF	tra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMSCHN ₂	Trimethylsilyldiazomethane
TMSCH ₂ N ₃	Trimethylsilylmethyl azide
T3P	propane phosphonic acid anhydride
TRIS	tris (hydroxymethyl) aminomethane
pTsOH	p-toluenesulfonic acid

IV. BIOLOGY

Lysophospholipids are membrane-derived bioactive lipid mediators. Lysophospholipids include, but are not limited to, lysophosphatidic acid (1-acyl-2-hydroxy-*sn*-glycero-3-phosphate; LPA), sphingosine 1-phosphate (S1P),
 5 lysophosphatidylcholine (LPC), and sphingosylphosphorylcholine (SPC).

Lysophospholipids affect fundamental cellular functions that include cellular proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis. These functions influence many biological processes that include neurogenesis, angiogenesis, wound healing, immunity, and carcinogenesis.

5 LPA acts through sets of specific G protein-coupled receptors (GPCRs) in an autocrine and paracrine fashion. LPA binding to its cognate GPCRs (LPA₁, LPA₂, LPA₃, LPA₄, LPA₅, LPA₆) activates intracellular signaling pathways to produce a variety of biological responses.

10 Lysophospholipids, such as LPA, are quantitatively minor lipid species compared to their major phospholipid counterparts (*e.g.*, phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin). LPA has a role as a biological effector molecule, and has a diverse range of physiological actions such as, but not limited to, effects on blood pressure, platelet activation, and smooth muscle contraction, and a variety of cellular effects, which include cell growth, cell rounding, neurite retraction, and
15 actin stress fiber formation and cell migration. The effects of LPA are predominantly receptor mediated.

Activation of the LPA receptors (LPA₁, LPA₂, LPA₃, LPA₄, LPA₅, LPA₆) with LPA mediates a range of downstream signaling cascades. These include, but are not limited to, mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC)
20 inhibition/activation, phospholipase C (PLC) activation/ Ca^{2+} mobilization, arachidonic acid release, Akt/PKB activation, and the activation of small GTPases, Rho, ROCK, Rac, and Ras. Other pathways that are affected by LPA receptor activation include, but are not limited to, cyclic adenosine monophosphate (cAMP), cell division cycle 42/GTP-binding protein (Cdc42), proto-oncogene serine/threonine-protein kinase Raf (c-RAF), proto-
25 oncogene tyrosine-protein kinase Src (c-src), extracellular signal-regulated kinase (ERK), focal adhesion kinase (FAK), guanine nucleotide exchange factor (GEF), glycogen synthase kinase 3b (GSK3b), c-jun amino-terminal kinase (JNK), MEK, myosin light chain II (MLC II), nuclear factor kB (NF-kB), N-methyl-D-aspartate (NMDA) receptor activation, phosphatidylinositol 3-kinase (PI3K), protein kinase A (PKA), protein kinase
30 C (PKC), ras-related C3 botulinum toxin substrate 1 (RAC1). The actual pathway and realized end point are dependent on a range of variables that include receptor usage, cell type, expression level of a receptor or signaling protein, and LPA concentration. Nearly

all mammalian cells, tissues and organs co-express several LPA-receptor subtypes, which indicates that LPA receptors signal in a cooperative manner. LPA₁, LPA₂, and LPA₃ share high amino acid sequence similarity.

LPA is produced from activated platelets, activated adipocytes, neuronal cells, and other cell types. Serum LPA is produced by multiple enzymatic pathways that involve monoacylglycerol kinase, phospholipase A₁, secretory phospholipase A₂, and lysophospholipase D (lysoPLD), including autotaxin. Several enzymes are involved in LPA degradation: lysophospholipase, lipid phosphate phosphatase, and LPA acyl transferase such as endophilin. LPA concentrations in human serum are estimated to be 1–5 μM. Serum LPA is bound to albumin, low-density lipoproteins, or other proteins, which possibly protect LPA from rapid degradation. LPA molecular species with different acyl chain lengths and saturation are naturally occurring, including 1-palmitoyl (16:0), 1-palmitoleoyl (16:1), 1-stearoyl (18:0), 1-oleoyl (18:1), 1-linoleoyl (18:2), and 1-arachidonyl (20:4) LPA. Quantitatively minor alkyl LPA has biological activities similar to acyl LPA, and different LPA species activate LPA receptor subtypes with varied efficacies.

LPA RECEPTORS

LPA₁ (previously called VZG-1/EDG-2/mrec1.3) couples with three types of G proteins, G_{i/o}, G_q, and G_{12/13}. Through activation of these G proteins, LPA induces a range of cellular responses through LPA₁ including but not limited to: cell proliferation, serum-response element (SRE) activation, mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC) inhibition, phospholipase C (PLC) activation, Ca²⁺ mobilization, Akt activation, and Rho activation.

Wide expression of LPA₁ is observed in adult mice, with clear presence in testis, brain, heart, lung, small intestine, stomach, spleen, thymus, and skeletal muscle. Similarly, human tissues also express LPA₁; it is present in brain, heart, lung, placenta, colon, small intestine, prostate, testis, ovary, pancreas, spleen, kidney, skeletal muscle, and thymus.

LPA₂ (EDG-4) also couples with three types of G proteins, G_{i/o}, G_q, and G_{12/13}, to mediate LPA-induced cellular signaling. Expression of LPA₂ is observed in the testis, kidney, lung, thymus, spleen, and stomach of adult mice and in the human testis,

pancreas, prostate, thymus, spleen, and peripheral blood leukocytes. Expression of LPA₂ is upregulated in various cancer cell lines, and several human LPA₂ transcriptional variants with mutations in the 3'-untranslated region have been observed. Targeted deletion of LPA₂ in mice has not shown any obvious phenotypic abnormalities, but has demonstrated a significant loss of normal LPA signaling (e.g., PLC activation, Ca²⁺ mobilization, and stress fiber formation) in primary cultures of mouse embryonic fibroblasts (MEFs). Creation of *lpa1(-/-) lpa2(-/-)* double-null mice has revealed that many LPA-induced responses, which include cell proliferation, AC inhibition, PLC activation, Ca²⁺ mobilization, JNK and Akt activation, and stress fiber formation, are absent or severely reduced in double-null MEFs. All these responses, except for AC inhibition (AC inhibition is nearly abolished in LPA₁ (-/-) MEFs), are only partially affected in either LPA₁ (-/-) or LPA₂ (-/-) MEFs. LPA₂ contributes to normal LPA-mediated signaling responses in at least some cell types (Choi *et al*, *Biochemica et Biophysica Acta* 2008, 1781, p531-539).

LPA₃ (EDG-7) is distinct from LPA₁ and LPA₂ in its ability to couple with G_{i/o} and G_q but not G_{12/13} and is much less responsive to LPA species with saturated acyl chains. LPA₃ can mediate pleiotropic LPA-induced signaling that includes PLC activation, Ca²⁺ mobilization, AC inhibition/activation, and MAPK activation. Overexpression of LPA₃ in neuroblastoma cells leads to neurite elongation, whereas that of LPA₁ or LPA₂ results in neurite retraction and cell rounding when stimulated with LPA. Expression of LPA₃ is observed in adult mouse testis, kidney, lung, small intestine, heart, thymus, and brain. In humans, it is found in the heart, pancreas, prostate, testis, lung, ovary, and brain (frontal cortex, hippocampus, and amygdala).

LPA₄ (p2y₉/GPR23) is of divergent sequence compared to LPA₁, LPA₂, and LPA₃ with closer similarity to the platelet-activating factor (PAF) receptor. LPA₄ mediates LPA induced Ca²⁺ mobilization and cAMP accumulation, and functional coupling to the G protein G_s for AC activation, as well as coupling to other G proteins. The LPA₄ gene is expressed in the ovary, pancreas, thymus, kidney and skeletal muscle.

LPA₅ (GPR92) is a member of the purinocluster of GPCRs and is structurally most closely related to LPA₄. LPA₅ is expressed in human heart, placenta, spleen, brain, lung and gut. LPA₅ also shows very high expression in the CD8⁺ lymphocyte compartment of the gastrointestinal tract.

LPA₆ (p2y5) is a member of the purinocluster of GPCRs and is structurally most closely related to LPA₄. LPA₆ is an LPA receptor coupled to the G12/13-Rho signaling pathways and is expressed in the inner root sheaths of human hair follicles.

5 **Illustrative Biological Activity**

Wound Healing

Normal wound healing occurs by a highly coordinated sequence of events in which cellular, soluble factors and matrix components act in concert to repair the injury. The healing response can be described as taking place in four broad, overlapping
10 phases—hemostasis, inflammation, proliferation, and remodeling. Many growth factors and cytokines are released into a wound site to initiate and perpetuate wound healing processes.

When wounded, damaged blood vessels activate platelets. The activated platelets play pivotal roles in subsequent repair processes by releasing bioactive mediators to
15 induce cell proliferation, cell migration, blood coagulation, and angiogenesis. LPA is one such mediator that is released from activated platelets; this induces platelet aggregation along with mitogenic/migration effects on the surrounding cells, such as endothelial cells, smooth muscle cells, fibroblasts, and keratinocytes.

Topical application of LPA to cutaneous wounds in mice promotes repair
20 processes (wound closure and increased neoepithelial thickness) by increasing cell proliferation/ migration without affecting secondary inflammation.

Activation of dermal fibroblasts by growth factors and cytokines leads to their subsequent migration from the edges of the wound into the provisional matrix formed by the fibrin clot whereupon the fibroblasts proliferate and start to restore the dermis by
25 secreting and organizing the characteristic dermal extracellular matrix (ECM). The increasing number of fibroblasts within the wound and continuous precipitation of ECM enhances matrix rigidity by applying small tractional forces to the newly formed granulation tissue. The increase in mechanical stress, in conjunction with transforming growth factor β (TGF β), induces α -smooth muscle actin (α -SMA) expression and the
30 subsequent transformation of fibroblasts into myofibroblasts. Myofibroblasts facilitate granulation tissue remodeling via myofibroblast contraction and through the production of ECM components.

LPA regulates many important functions of fibroblasts in wound healing, including proliferation, migration, differentiation and contraction. Fibroblast proliferation is required in wound healing in order to fill an open wound. In contrast, fibrosis is characterized by intense proliferation and accumulation of myofibroblasts that actively synthesize ECM and proinflammatory cytokines. LPA can either increase or suppress the proliferation of cell types important in wound healing, such as epithelial and endothelial cells (EC), macrophages, keratinocytes, and fibroblasts. A role for LPA₁ in LPA-induced proliferation was provided by the observation that LPA-stimulated proliferation of fibroblasts isolated from LPA₁ receptor null mice was attenuated (Mills *et al*, *Nat Rev. Cancer* 2003; 3: 582-591). LPA induces cytoskeletal changes that are integral to fibroblast adhesion, migration, differentiation and contraction.

Fibrosis

Tissue injury initiates a complex series of host wound-healing responses; if successful, these responses restore normal tissue structure and function. If not, these responses can lead to tissue fibrosis and loss of function.

For the majority of organs and tissues the development of fibrosis involves a multitude of events and factors. Molecules involved in the development of fibrosis include proteins or peptides (profibrotic cytokines, chemokines, metalloproteinases etc.) and phospholipids. Phospholipids involved in the development of fibrosis include platelet activating factor (PAF), phosphatidyl choline, sphingosine-1 phosphate (S1P) and lysophosphatidic acid (LPA).

A number of muscular dystrophies are characterized by a progressive weakness and wasting of musculature, and by extensive fibrosis. It has been shown that LPA treatment of cultured myoblasts induced significant expression of connective tissue growth factor (CTGF). CTGF subsequently induces collagen, fibronectin and integrin expression and induces dedifferentiation of these myoblasts. Treatment of a variety of cell types with LPA induces reproducible and high level induction of CTGF (J.P. Pradere, *et al.*, LPA₁ receptor activation promotes renal interstitial fibrosis, *J. Am. Soc. Nephrol.* 18 (2007) 3110–3118; N. Wiedmaier, *et al.*, *Int J Med Microbiol*; 298(3-4):231-43, 2008). CTGF is a profibrotic cytokine, signaling down-stream and in parallel with TGFβ.

CTGF expression by gingival epithelial cells, which are involved in the development of gingival fibromatosis, was found to be exacerbated by LPA treatment (A. Kantarci, *et al.*, *J. Pathol.* 210 (2006) 59–66).

LPA is associated with the progression of liver fibrosis. *In vitro*, LPA induces
5 stellate cell and hepatocyte proliferation. These activated cells are the main cell type responsible for the accumulation of ECM in the liver. Furthermore, LPA plasma levels rise during CCl₄-induced liver fibrosis in rodents, or in hepatitis C virus-induced liver fibrosis in humans (N. Watanabe, *et al.*, Plasma lysophosphatidic acid level and serum autotaxin activity are increased in liver injury in rats in relation to its severity, *Life Sci.* 81
10 (2007) 1009–1015; N. Watanabe, *et al.*, *J. Clin. Gastroenterol.* 41 (2007) 616–623).

An increase of phospholipid concentrations in the bronchoalveolar lavage fluid in rabbits and rodents injected with bleomycin has been reported (K. Kuroda, *et al.*, Phospholipid concentration in lung lavage fluid as biomarker for pulmonary fibrosis, *Inhal. Toxicol.* 18 (2006) 389–393; K. Yasuda, *et al.*, *Lung* 172 (1994) 91–102).

LPA is associated with heart disease and myocardial remodeling. Serum LPA
15 levels are increased after myocardial infarction in patients and LPA stimulates rat cardiac fibroblast proliferation and collagen production (*Chen et al. FEBS Lett.* 2006 Aug 21;580(19):4737-45).

20 **Pulmonary Fibrosis**

In the lung, aberrant wound healing responses to injury contribute to the pathogenesis of fibrotic lung diseases. Fibrotic lung diseases, such as idiopathic pulmonary fibrosis (IPF), are associated with high morbidity and mortality.

LPA is an important mediator of fibroblast recruitment in pulmonary fibrosis.
25 LPA and LPA₁ play key pathogenic roles in pulmonary fibrosis. Fibroblast chemoattractant activity plays an important role in the lungs in patients with pulmonary fibrosis. Profibrotic effects of LPA₁-receptor stimulation is explained by LPA₁-receptor-mediated vascular leakage and increased fibroblast recruitment, both profibrotic events. The LPA-LPA₁ pathway has a role in mediating fibroblast migration and vascular leakage
30 in IPF. The end result is the aberrant healing process that characterizes this fibrotic condition.

The LPA₁ receptor is the LPA receptor most highly expressed on fibroblasts obtained from patients with IPF. Furthermore, BAL obtained from IPF patients induced

chemotaxis of human foetal lung fibroblasts that was blocked by the dual LPA₁- LPA₃ receptor antagonist Ki16425. In an experimental bleomycin-induced lung injury mouse model, it was shown that LPA levels were high in bronchoalveolar lavage samples compared with unexposed controls. LPA₁ knockout mice are protected from fibrosis after
 5 bleomycin challenge with reduced fibroblast accumulation and vascular leakage. In human subjects with IPF, high LPA levels were observed in bronchoalveolar lavage samples compared with healthy controls. Increased fibroblast chemotactic activity in these samples was inhibited by the Ki16425 indicating that fibroblast migration is mediated by the LPA-LPA receptor(s) pathway (Tager *et al. Nature Medicine*, **2008**, *14*,
 10 45-54).

The LPA-LPA₁ pathway is crucial in fibroblast recruitment and vascular leakage in pulmonary fibrosis.

Activation of latent TGF- β by the α v β 6 integrin plays a critical role in the development of lung injury and fibrosis (*Munger et al. Cell*, vol. 96, 319-328, 1999). LPA
 15 induces α v β 6-mediated TGF- β activation on human lung epithelial cells (*Xu et al. Am. J. Pathology*, **2009**, *174*, 1264-1279). The LPA-induced α v β 6-mediated TGF- β activation is mediated by the LPA₂ receptor. Expression of the LPA₂ receptor is increased in epithelial cells and mesenchymal cells in areas of lung fibrosis from IPF patients compared to normal human lung tissue. The LPA-LPA₂ pathway contributes to the activation of the
 20 TGF- β pathway in pulmonary fibrosis. In some embodiments, compounds that inhibit LPA₂ show efficacy in the treatment of lung fibrosis. In some embodiments, compounds that inhibit both LPA₁ and LPA₂ show improved efficacy in the treatment of lung fibrosis compared to compounds which inhibit only LPA₁ or LPA₂.

25 **Renal Fibrosis**

LPA and LPA₁ are involved in the etiology of kidney fibrosis. LPA has effects on both proliferation and contraction of glomerular mesangial cells and thus has been implicated in proliferative glomerulonephritis (C.N. Inoue, *et al., Clin. Sci. (Colch.)* **1999**,
 30 *96*, 431-436). In an animal model of renal fibrosis [unilateral ureteral obstruction (UUO)], it was found that renal LPA receptors are expressed under basal conditions with an expression order of LPA₂>LPA₃=LPA₁>>LPA₄. This model mimics in an accelerated manner the development of renal fibrosis including renal inflammation, fibroblast

activation and accumulation of extracellular matrix in the tubulointerstitium. UUU significantly induced LPA₁-receptor expression. This was paralleled by renal LPA production (3.3 fold increase) in conditioned media from kidney explants. Contra-lateral kidneys exhibited no significant changes in LPA release and LPA-receptors expression.

5 This shows that a prerequisite for an action of LPA in fibrosis is met: production of a ligand (LPA) and induction of one of its receptors (the LPA₁ receptor) (J.P. Pradere *et al.*, *Biochimica et Biophysica Acta*, **2008**, 1781, 582-587).

In mice where the LPA₁ receptor was knocked out (LPA₁ ^{-/-}), the development of renal fibrosis was significantly attenuated. UUU mice treated with the LPA receptor antagonist Ki16425 closely resembled the profile of LPA₁ ^{-/-} mice.

LPA can participate in intraperitoneal accumulation of monocyte/macrophages and LPA can induce expression of the profibrotic cytokine CTGF in primary cultures of human fibroblasts (J.S. Koh, *et al.*, *J. Clin. Invest.*, **1998**, 102, 716-727).

LPA treatment of a mouse epithelial renal cell line, MCT, induced a rapid increase
15 in the expression of the profibrotic cytokine CTGF. CTGF plays a crucial role in UUU-induced tubulointerstitial fibrosis (TIF), and is involved in the profibrotic activity of TGFβ. This induction was almost completely suppressed by co-treatment with the LPA-receptor antagonist Ki16425. In one aspect, the profibrotic activity of LPA in kidney results from a direct action of LPA on kidney cells involving induction of CTGF.

20

Hepatic fibrosis

LPA is implicated in liver disease and fibrosis. Plasma LPA levels and serum autotaxin (enzyme responsible for LPA production) are elevated in hepatitis patients and animal models of liver injury in correlation with increased fibrosis. LPA also regulates
25 liver cell function. LPA₁ and LPA₂ receptors are expressed by mouse hepatic stellate cells and LPA stimulates migration of hepatic myofibroblasts.

Ocular Fibrosis

LPA is involved in wound healing in the eye. LPA₁ and LPA₃ receptors are
30 detectable in the normal rabbit corneal epithelial cells, keratocytes and endothelial cells and LPA₁ and LPA₃ expression are increased in corneal epithelial cells following injury.

LPA and its homologues are present in the aqueous humor and the lacrimal gland fluid of the rabbit eye and these levels are increased in a rabbit corneal injury model.

LPA induces actin stress fiber formation in rabbit corneal endothelial and epithelial cells and promotes contraction corneal fibroblasts. LPA also stimulates
5 proliferation of human retinal pigmented epithelial cells

Cardiac fibrosis

LPA is implicated in myocardial infarction and cardiac fibrosis. Serum LPA levels are increased in patients following myocardial infarction (MI) and LPA stimulates
10 proliferation and collagen production (fibrosis) by rat cardiac fibroblasts. Both LPA₁ and LPA₃ receptors are highly expressed in human heart tissue.

Treatment of Fibrosis

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or
15 solvate thereof, is used to treat or prevent fibrosis in a mammal. In one aspect, a compound of Formulas (I), or a pharmaceutically acceptable salt or solvate thereof, is used to treat fibrosis of an organ or tissue in a mammal. In one aspect is a method for preventing a fibrosis condition in a mammal, the method comprising administering to the mammal at risk of developing one or more fibrosis conditions a therapeutically effective
20 amount of a compound of Formulas (I), or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the mammal has been exposed to one or more environmental conditions that are known to increase the risk of fibrosis of an organ or tissue. In one aspect, the mammal has been exposed to one or more environmental conditions that are known to increase the risk of lung, liver or kidney fibrosis. In one aspect, the mammal has
25 a genetic predisposition of developing fibrosis of an organ or tissue. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is administered to a mammal to prevent or minimize scarring following injury. In one aspect, injury includes surgery.

The terms “fibrosis” or “fibrosing disorder,” as used herein, refers to conditions
30 that are associated with the abnormal accumulation of cells and/or fibronectin and/or collagen and/or increased fibroblast recruitment and include but are not limited to fibrosis

of individual organs or tissues such as the heart, kidney, liver, joints, lung, pleural tissue, peritoneal tissue, skin, cornea, retina, musculoskeletal and digestive tract.

Exemplary diseases, disorders, or conditions that involve fibrosis include, but are not limited to: Lung diseases associated with fibrosis, *e.g.*, idiopathic pulmonary fibrosis, pulmonary fibrosis secondary to systemic inflammatory disease such as rheumatoid
5 arthritis, scleroderma, lupus, cryptogenic fibrosing alveolitis, radiation induced fibrosis, chronic obstructive pulmonary disease (COPD), scleroderma, chronic asthma, silicosis, asbestos induced pulmonary or pleural fibrosis, acute lung injury and acute respiratory distress (including bacterial pneumonia induced, trauma induced, viral pneumonia
10 induced, ventilator induced, non-pulmonary sepsis induced, and aspiration induced); Chronic nephropathies associated with injury/fibrosis (kidney fibrosis), *e.g.*, glomerulonephritis secondary to systemic inflammatory diseases such as lupus and scleroderma, diabetes, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, allograft and Alport; Gut fibrosis, *e.g.*, scleroderma, and
15 radiation induced gut fibrosis; Liver fibrosis, *e.g.*, cirrhosis, alcohol induced liver fibrosis, nonalcoholic steatohepatitis (NASH), biliary duct injury, primary biliary cirrhosis, infection or viral induced liver fibrosis (*e.g.*, chronic HCV infection), and autoimmune hepatitis; Head and neck fibrosis, *e.g.*, radiation induced; Corneal scarring, *e.g.*, LASIK (laser-assisted in situ keratomileusis), corneal transplant, and trabeculectomy;
20 Hypertrophic scarring and keloids, *e.g.*, burn induced or surgical; and other fibrotic diseases, *e.g.*, sarcoidosis, scleroderma, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, mixed connective tissue disease, and Peyronie's disease.

In one aspect, a mammal suffering from one of the following non-limiting
25 exemplary diseases, disorders, or conditions will benefit from therapy with a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof: atherosclerosis, thrombosis, heart disease, vasculitis, formation of scar tissue, restenosis, phlebitis, COPD (chronic obstructive pulmonary disease), pulmonary hypertension, pulmonary fibrosis, pulmonary inflammation, bowel adhesions, bladder fibrosis and cystitis, fibrosis of the
30 nasal passages, sinusitis, inflammation mediated by neutrophils, and fibrosis mediated by fibroblasts.

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is administered to a mammal with fibrosis of an organ or tissue or with a predisposition of developing fibrosis of an organ or tissue with one or more other agents that are used to treat fibrosis. In one aspect, the one or more agents include

5 corticosteroids. In one aspect, the one or more agents include immunosuppressants. In one aspect, the one or more agents include B-cell antagonists. In one aspect, the one or more agents include uteroglobin.

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used to treat a dermatological disorders in a mammal. The term
10 “dermatological disorder,” as used herein refers to a skin disorder. Such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, psoriasis, scleroderma, psoriatic lesions, dermatitis, contact dermatitis, eczema, urticaria, rosacea, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, Sjogren-Larsson
15 Syndrome, urticaria. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used to treat systemic sclerosis.

Pain

Since LPA is released following tissue injury, LPA₁ plays an important role in the
20 initiation of neuropathic pain. LPA₁, unlike LPA₂ or LPA₃, is expressed in both dorsal root ganglion (DRG) and dorsal root neurons. Using the antisense oligodeoxynucleotide (AS-ODN) for LPA₁ and LPA₁-null mice, it was found that LPA-induced mechanical allodynia and hyperalgesia is mediated in an LPA₁-dependent manner. LPA₁ and downstream Rho–ROCK activation play a role in the initiation of neuropathic pain
25 signaling. Pretreatment with Clostridium botulinum C3 exoenzyme (BoTXC3, Rho inhibitor) or Y-27632 (ROCK inhibitor) completely abolished the allodynia and hyperalgesia in nerve-injured mice. LPA also induced demyelination of the dorsal root, which was prevented by BoTXC3. The dorsal root demyelination by injury was not observed in LPA₁-null mice or AS-ODN injected wild-type mice. LPA signaling appears
30 to induce important neuropathic pain markers such as protein kinase C γ (PKC γ) and a voltage-gated calcium channel α 2 δ 1 subunit (Ca α 2 δ 1) in an LPA₁ and Rho-dependent

manner (M. Inoue, *et al.*, Initiation of neuropathic pain requires lysophosphatidic acid receptor signaling, *Nat. Med.* 10 (2004) 712–718).

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of pain in a mammal. In one aspect, the pain is acute pain or chronic pain. In another aspect, the pain is neuropathic pain.

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of fibromyalgia. In one aspect, fibromyalgia stems from the formation of fibrous scar tissue in contractile (voluntary) muscles. Fibrosis binds the tissue and inhibits blood flow, resulting in pain.

10

Cancer

Lysophospholipid receptor signaling plays a role in the etiology of cancer. Lysophosphatidic acid (LPA) and its G protein-coupled receptors (GPCRs) LPA₁, LPA₂, and/or LPA₃ play a role in the development of several types of cancers. The initiation, progression and metastasis of cancer involve several concurrent and sequential processes including cell proliferation and growth, survival and anti-apoptosis, migration of cells, penetration of foreign cells into defined cellular layers and/or organs, and promotion of angiogenesis. The control of each of these processes by LPA signaling in physiological and pathophysiological conditions underscores the potential therapeutic usefulness of modulating LPA signaling pathways for the treatment of cancer, especially at the level of the LPA receptors or ATX/lysoPLD. Autotaxin (ATX) is a prometastatic enzyme initially isolated from the conditioned medium of human melanoma cells that stimulates a myriad of biological activities, including angiogenesis and the promotion of cell growth, migration, survival, and differentiation through the production of LPA (*Mol Cancer Ther* 2008;7(10):3352–62).

LPA signals through its own GPCRs leading to activation of multiple downstream effector pathways. Such downstream effector pathways play a role in cancer. LPA and its GPCRs are linked to cancer through major oncogenic signaling pathways.

LPA contributes to tumorigenesis by increasing motility and invasiveness of cells. LPA has been implicated in the initiation or progression of ovarian cancer. LPA is present at significant concentrations (2–80 μM) in the ascitic fluid of ovarian cancer patients. Ovarian cancer cells constitutively produce increased amounts of LPA as compared to

30

normal ovarian surface epithelial cells, the precursor of ovarian epithelial cancer.

Elevated LPA levels are also detected in plasma from patients with early-stage ovarian cancers compared with controls. LPA receptors (LPA₂ and LPA₃) are also overexpressed in ovarian cancer cells as compared to normal ovarian surface epithelial cells. LPA

5 stimulates Cox-2 expression through transcriptional activation and post-transcriptional enhancement of Cox-2 mRNA in ovarian cancer cells. Prostaglandins produced by Cox-2 have been implicated in a number of human cancers and pharmacological inhibition of Cox-2 activity reduces colon cancer development and decreases the size and number of adenomas in patients with familial adenomatous polyposis. LPA has also been implicated
10 in the initiation or progression of prostate cancer, breast cancer, melanoma, head and neck cancer, bowel cancer (colorectal cancer), thyroid cancer and other cancers (*Gardell et al, Trends in Molecular Medicine*, vol. 12, no. 2, p 65-75, 2006; *Ishii et al, Annu. Rev. Biochem*, 73, 321-354, 2004; *Mills et al., Nat. Rev. Cancer*, 3, 582-591, 2003; *Murph et al., Biochimica et Biophysica Acta*, 1781, 547-557, 2008).

15 The cellular responses to LPA are mediated through the lysophosphatidic acid receptors. For example, LPA receptors mediate both migration of and invasion by pancreatic cancer cell lines: an antagonist of LPA₁ and LPA₃ (Ki16425) and LPA₁-specific siRNA effectively blocked in vitro migration in response to LPA and peritoneal fluid (ascites) from pancreatic cancer patients; in addition, Ki16425 blocked the LPA-
20 induced and ascites-induced invasion activity of a highly peritoneal metastatic pancreatic cancer cell line (*Yamada et al, J. Biol. Chem.*, 279, 6595-6605, 2004).

Colorectal carcinoma cell lines show significant expression of LPA₁ mRNA and respond to LPA by cell migration and production of angiogenic factors. Overexpression of LPA receptors has a role in the pathogenesis of thyroid cancer. LPA₃ was originally
25 cloned from prostate cancer cells, concordant with the ability of LPA to induce autocrine proliferation of prostate cancer cells.

LPA has stimulatory roles in cancer progression in many types of cancer. LPA is produced from and induces proliferation of prostate cancer cell lines. LPA induces human colon carcinoma DLD1 cell proliferation, migration, adhesion, and secretion of
30 angiogenic factors through LPA₁ signaling. In other human colon carcinoma cells lines (HT29 and WiDR), LPA enhances cell proliferation and secretion of angiogenic factors. In other colon cancer cell lines, LPA₂ and LPA₃ receptor activation results in proliferation

of the cells. The genetic or pharmacological manipulation of LPA metabolism, specific blockade of receptor signaling, and/or inhibition of downstream signal transduction pathways, represent approaches for cancer therapies.

It has been reported that LPA and other phospholipids stimulate expression of interleukin-8 (IL-8) in ovarian cancer cell lines. In some embodiments, high concentrations of IL-8 in ovarian cancer correlate with poor initial response to chemotherapy and with poor prognosis, respectively. In animal models, expression of IL-8 and other growth factors such as vascular endothelial growth factor (VEGF) is associated with increased tumorigenicity, ascites formation, angiogenesis, and invasiveness of ovarian cancer cells. In some aspects, IL-8 is an important modulator of cancer progression, drug resistance, and prognosis in ovarian cancer. In some embodiments, a compound of Formula (I) inhibits or reduces IL-8 expression in ovarian cancer cell lines.

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of cancer. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of malignant and benign proliferative disease. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used to prevent or reduce proliferation of tumor cells, invasion and metastasis of carcinomas, pleural mesothelioma (Yamada, *Cancer Sci.*, 2008, 99(8), 1603-1610) or peritoneal mesothelioma, cancer pain, bone metastases (Boucharaba *et al*, *J. Clin. Invest.*, 2004, 114(12), 1714-1725; Boucharaba *et al*, *Proc. Natl. acad. Sci.*, 2006, 103(25) 9643-9648). In one aspect is a method of treating cancer in a mammal, the method comprising administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a second therapeutic agent, wherein the second therapeutic agent is an anti-cancer agent.

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

cancer) or hematological tumors (such as the leukemias) at any stage of the disease with or without metastases.

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

syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, Wilms tumor.

The increased concentrations of LPA and vesicles in ascites from ovarian cancer patients and breast cancer effusions indicate that it could be an early diagnostic marker, a prognostic indicator or an indicator of response to therapy (Mills *et al*, *Nat. Rev. Cancer.*, 3, 582-591, 2003; Sutphen *et al.*, *Cancer Epidemiol. Biomarkers Prev.* 13, 1185-1191, 2004). LPA concentrations are consistently higher in ascites samples than in matched plasma samples.

Respiratory and Allergic Disorders

In one aspect, LPA is a contributor to the pathogenesis of respiratory diseases. In one aspect the respiratory disease is asthma. Proinflammatory effects of LPA include degranulation of mast cells, contraction of smooth-muscle cells and release of cytokines from dendritic cells. Airway smooth muscle cells, epithelial cells and lung fibroblasts all show responses to LPA. LPA induces the secretion of IL-8 from human bronchial epithelial cells. IL-8 is found in increased concentrations in BAL fluids from patients with asthma, chronic obstructive lung disease, pulmonary sarcoidosis and acute respiratory distress syndrome and IL-8 has been shown to exacerbate airway inflammation and airway remodeling of asthmatics. LPA₁, LPA₂ and LPA₃ receptors have all been shown to contribute to the LPA-induced IL-8 production. Studies cloning multiple GPCRs that are activated by LPA allowed the demonstration of the presence of mRNA for the LPA₁, LPA₂ and LPA₃ in the lung (J.J.A. Contos, *et al.*, *Mol. Pharmacol.* 58, 1188-1196, 2000).

The release of LPA from platelets activated at a site of injury and its ability to promote fibroblast proliferation and contraction are features of LPA as a mediator of wound repair. In the context of airway disease, asthma is an inflammatory disease where inappropriate airway “repair” processes lead to structural “remodeling” of the airway. In asthma, the cells of the airway are subject to ongoing injury due to a variety of insults, including allergens, pollutants, other inhaled environmental agents, bacteria and viruses, leading to the chronic inflammation that characterizes asthma.

In one aspect, in the asthmatic individual, the release of normal repair mediators, including LPA, is exaggerated or the actions of the repair mediators are inappropriately prolonged leading to inappropriate airway remodeling. Major structural features of the remodeled airway observed in asthma include a thickened lamina reticularis (the basement membrane-like structure just beneath the airway epithelial cells), increased numbers and activation of myofibroblasts, thickening of the smooth muscle layer, increased numbers of mucus glands and mucus secretions, and alterations in the connective tissue and capillary bed throughout the airway wall. In one aspect, LPA contributes to these structural changes in the airway. In one aspect, LPA is involved in acute airway hyperresponsiveness in asthma. The lumen of the remodeled asthmatic airway is narrower due to the thickening of the airway wall, thus decreasing airflow. In one aspect, LPA contributes to the long-term structural remodeling and the acute hyperresponsiveness of the asthmatic airway. In one aspect, LPA contributes to the hyperresponsiveness that is a primary feature of acute exacerbations of asthma.

In addition to the cellular responses mediated by LPA, several of the LPA signaling pathway components leading to these responses are relevant to asthma. EGF receptor upregulation is induced by LPA and is also seen in asthmatic airways (M. Amishima, *et al.*, *Am. J. Respir. Crit. Care Med.* 157, 1907–1912, 1998). Chronic inflammation is a contributor to asthma, and several of the transcription factors that are activated by LPA are known to be involved in inflammation (Ediger *et al.*, *Eur Respir J* 21:759-769, 2003).

In one aspect, the fibroblast proliferation and contraction and extracellular matrix secretion stimulated by LPA contributes to the fibroproliferative features of other airway diseases, such as the peribronchiolar fibrosis present in chronic bronchitis, emphysema, and interstitial lung disease. Emphysema is also associated with a mild fibrosis of the alveolar wall, a feature which is believed to represent an attempt to repair alveolar damage. In another aspect, LPA plays a role in the fibrotic interstitial lung diseases and obliterative bronchiolitis, where both collagen and myofibroblasts are increased. In another aspect, LPA is involved in several of the various syndromes that constitute chronic obstructive pulmonary disease.

Administration of LPA *in vivo* induces airway hyper-responsiveness, itch-scratch responses, infiltration and activation of eosinophils and neutrophils, vascular remodeling,

and nociceptive flexor responses. LPA also induces histamine release from mouse and rat mast cells. In an acute allergic reaction, histamine induces various responses, such as contraction of smooth muscle, plasma exudation, and mucus production. Plasma exudation is important in the airway, because the leakage and subsequent airway-wall edema contribute to the development of airway hyperresponsiveness. Plasma exudation progresses to conjunctival swelling in ocular allergic disorder and nasal blockage in allergic rhinitis (Hashimoto *et al.*, *J Pharmacol Sci* 100, 82 – 87, 2006). In one aspect, plasma exudation induced by LPA is mediated by histamine release from mast cells via one or more LPA receptors. In one aspect, the LPA receptor(s) include LPA₁ and/or LPA₃. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of various allergic disorders in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of respiratory diseases, disorders or conditions in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of asthma in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used in the treatment of chronic asthma in a mammal.

The term “respiratory disease,” as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, eustachian tubes, trachea, bronchi, lungs, related muscles (*e.g.*, diaphragm and intercostals), and nerves. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

The term “asthma” as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever

cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate cause.

In one aspect, presented herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the treatment or prevention of chronic obstructive pulmonary disease in a mammal comprising administering to the mammal at least once an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In addition, chronic obstructive pulmonary disease includes, but is not limited to, chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation, and cystic fibrosis.

Nervous System

The nervous system is a major locus for LPA₁ expression; there it is spatially and temporally regulated throughout brain development. Oligodendrocytes, the myelinating cells in the central nervous system (CNS), express LPA₁ in mammals. In addition, Schwann cells, the myelinating cells of the peripheral nervous system, also express LPA₁, which is involved in regulating Schwann cell survival and morphology. These observations identify important functions for receptor-mediated LPA signaling in neurogenesis, cell survival, and myelination.

Exposure of peripheral nervous system cell lines to LPA produces a rapid retraction of their processes resulting in cell rounding, which was, in part, mediated by polymerization of the actin cytoskeleton. In one aspect, LPA causes neuronal degeneration under pathological conditions when the blood-brain barrier is damaged and serum components leak into the brain (Moolenaar, *Curr. Opin. Cell Biol.* 7:203-10, 1995). Immortalized CNS neuroblast cell lines from the cerebral cortex also display retraction responses to LPA exposure through Rho activation and actomyosin interactions. In one aspect, LPA is associated with post-ischemic neural damage (*J. Neurochem.* 61, 340, 1993; *J. Neurochem.*, 70:66, 1998).

In one aspect, provided is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment or prevention of a nervous system disorder in a mammal. The term “nervous system disorder,” as used herein, refers to conditions that alter the structure or function of the brain, spinal cord or peripheral

nervous system, including but not limited to Alzheimer's Disease, cerebral edema, cerebral ischemia, stroke, multiple sclerosis, neuropathies, Parkinson's Disease, those found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as
5 degenerative disk disease and sciatica.

In one aspect, provided is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment or prevention of a CNS disorder in a mammal. CNS disorders include, but are not limited to, multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke, cerebral ischemia, retinal ischemia,
10 post-surgical cognitive dysfunction, migraine, peripheral neuropathy/neuropathic pain, spinal cord injury, cerebral edema and head injury.

Cardiovascular Disorders

Cardiovascular phenotypes observed after targeted deletion of lysophospholipid
15 receptors reveal important roles for lysophospholipid signaling in the development and maturation of blood vessels, formation of atherosclerotic plaques and maintenance of heart rate (Ishii, I. *et al. Annu. Rev. Biochem.* 73, 321–354, 2004). Angiogenesis, the formation of new capillary networks from pre-existing vasculature, is normally invoked in wound healing, tissue growth and myocardial angiogenesis after ischemic injury.
20 Peptide growth factors (*e.g.* vascular endothelial growth factor (VEGF)) and lysophospholipids control coordinated proliferation, migration, adhesion, differentiation and assembly of vascular endothelial cells (VECs) and surrounding vascular smooth-muscle cells (VSMCs). In one aspect, dysregulation of the processes mediating angiogenesis leads to atherosclerosis, hypertension, tumor growth, rheumatoid arthritis
25 and diabetic retinopathy (Osborne, N. and Stainier, D.Y. *Annu. Rev. Physiol.* 65, 23–43, 2003).

Downstream signaling pathways evoked by lysophospholipid receptors include Rac-dependent lamellipodia formation (*e.g.* LPA₁) and Rho-dependent stress-fiber formation (*e.g.* LPA₁), which is important in cell migration and adhesion. Dysfunction of
30 the vascular endothelium can shift the balance from vasodilatation to vasoconstriction and lead to hypertension and vascular remodeling, which are risk factors for atherosclerosis (Maguire, J.J. *et al., Trends Pharmacol. Sci.* 26, 448–454, 2005).

LPA contributes to both the early phase (barrier dysfunction and monocyte adhesion of the endothelium) and the late phase (platelet activation and intra-arterial thrombus formation) of atherosclerosis, in addition to its overall progression. In the early phase, LPA from numerous sources accumulates in lesions and activates its cognate
5 GPCRs (LPA₁ and LPA₃) expressed on platelets (Siess, W. *Biochim. Biophys. Acta* 1582, 204–215, 2002; Rother, E. *et al. Circulation* 108, 741–747, 2003). This triggers platelet shape change and aggregation, leading to intra-arterial thrombus formation and, potentially, myocardial infarction and stroke. In support of its atherogenic activity, LPA can also be a mitogen and motogen to VSMCs and an activator of endothelial cells and
10 macrophages. In one aspect, mammals with cardiovascular disease benefit from LPA receptor antagonists that prevent thrombus and neointima plaque formation.

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used to treat or prevent cardiovascular disease in mammal.

The term “cardiovascular disease,” as used herein refers to diseases affecting the
15 heart or blood vessels or both, including but not limited to: arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical,
20 or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue..

In one aspect, provided herein are methods for preventing or treating vasoconstriction, atherosclerosis and its sequelae myocardial ischemia, myocardial
25 infarction, aortic aneurysm, vasculitis and stroke comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition or medicament which includes a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

30 In one aspect, provided herein are methods for reducing cardiac reperfusion injury following myocardial ischemia and/or endotoxic shock comprising administering at least

once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, provided herein are methods for reducing the constriction of blood vessels in a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, provided herein are methods for lowering or preventing an increase in blood pressure of a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

Inflammation

LPA has been shown to regulate immunological responses by modulating activities/functions of immune cells such as T-/B-lymphocytes and macrophages. In activated T cells, LPA activates IL-2 production/cell proliferation through LPA₁ (Gardell et al, *TRENDS in Molecular Medicine* Vol.12 No.2 February 2006). Expression of LPA-induced inflammatory response genes is mediated by LPA₁ and LPA₃ (*Biochem Biophys Res Commun.* 363(4):1001-8, 2007). In addition, LPA modulates the chemotaxis of inflammatory cells (*Biochem Biophys Res Commun.*, 1993, 15;193(2), 497). The proliferation and cytokine-secreting activity in response to LPA of immune cells (*J. Immunol.* 1999, 162, 2049), platelet aggregation activity in response to LPA, acceleration of migration activity in monocytes, activation of NF- κ B in fibroblast, enhancement of fibronectin-binding to the cell surface, and the like are known. Thus, LPA is associated with various inflammatory/immune diseases.

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used to treat or prevent inflammation in a mammal. In one aspect, antagonists of LPA₁ and/or LPA₃ find use in the treatment or prevention of inflammatory/immune disorders in a mammal. In one aspect, the antagonist of LPA₁ is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

Examples of inflammatory/immune disorders include psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma,

eczema, allogeneic or xenogeneic transplantation (organ, bone marrow, stem cells and other cells and tissues) graft rejection, graft-versus-host disease, lupus erythematosus, inflammatory disease, type I diabetes, pulmonary fibrosis, dermatomyositis, Sjogren's syndrome, thyroiditis (*e.g.*, Hashimoto's and autoimmune thyroiditis), myasthenia gravis, 5 autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis and atopic dermatitis.

Other Diseases, Disorders or Conditions

In accordance with one aspect, are methods for treating, preventing, reversing, 10 halting or slowing the progression of LPA-dependent or LPA-mediated diseases or conditions once it becomes clinically evident, or treating the symptoms associated with or related to LPA-dependent or LPA-mediated diseases or conditions, by administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the subject already has a LPA-dependent or LPA- 15 mediated disease or condition at the time of administration, or is at risk of developing a LPA-dependent or LPA-mediated disease or condition.

In certain aspects, the activity of LPA₁ in a mammal is directly or indirectly modulated by the administration of (at least once) a therapeutically effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate 20 thereof. Such modulation includes, but is not limited to, reducing and/or inhibiting the activity of LPA₁. In additional aspects, the activity of LPA in a mammal is directly or indirectly modulated, including reducing and/or inhibiting, by the administration of (at least once) a therapeutically effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. Such modulation includes, but is not 25 limited to, reducing and/or inhibiting the amount and/or activity of a LPA receptor. In one aspect, the LPA receptor is LPA₁.

In one aspect, LPA has a contracting action on bladder smooth muscle cell isolated from bladder, and promotes growth of prostate-derived epithelial cell (*J. Urology*, **1999**, 162, 1779-1784; *J. Urology*, **2000**, 163, 1027-1032). In another aspect, 30 LPA contracts the urinary tract and prostate *in vitro* and increases intraurethral pressure *in vivo* (WO 02/062389).

In certain aspects, are methods for preventing or treating eosinophil and/or basophil and/or dendritic cell and/or neutrophil and/or monocyte and/or T-cell recruitment comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In certain aspects, are methods for the treatment of cystitis, including, *e.g.*, interstitial cystitis, comprising administering at least once to the mammal a therapeutically effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In accordance with one aspect, methods described herein include the diagnosis or determination of whether or not a patient is suffering from a LPA-dependent or LPA-mediated disease or condition by administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, and determining whether or not the patient responds to the treatment.

In one aspect provided herein are compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, which are antagonists of LPA₁, and are used to treat patients suffering from one or more LPA-dependent or LPA-mediated conditions or diseases, including, but not limited to, lung fibrosis, kidney fibrosis, liver fibrosis, scarring, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, arthritis, allergy, psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, pain, proliferative disorders and inflammatory conditions. In some embodiments, LPA-dependent conditions or diseases include those wherein an absolute or relative excess of LPA is present and/or observed.

In any of the aforementioned aspects the LPA-dependent or LPA-mediated diseases or conditions include, but are not limited to, organ fibrosis, asthma, allergic disorders, chronic obstructive pulmonary disease, pulmonary hypertension, lung or pleural fibrosis, peritoneal fibrosis, arthritis, allergy, cancer, cardiovascular disease, ult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, and cancer.

In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is used to improve the corneal sensitivity decrease caused by corneal

operations such as laser-assisted in situ keratomileusis (LASIK) or cataract operation, corneal sensitivity decrease caused by corneal degeneration, and dry eye symptom caused thereby.

5 In one aspect, presented herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the treatment or prevention of ocular inflammation and allergic conjunctivitis, vernal keratoconjunctivitis, and papillary conjunctivitis in a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

10 In one aspect, presented herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the treatment or prevention of Sjogren disease or inflammatory disease with dry eyes in a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

15 In one aspect, LPA and LPA receptors (*e.g.* LPA₁) are involved in the pathogenesis of osteoarthritis (Kotani *et al*, *Hum. Mol. Genet.*, **2008**, *17*, 1790-1797). In one aspect, presented herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the treatment or prevention of osteoarthritis in a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

20 In one aspect, LPA receptors (*e.g.* LPA₁, LPA₃) contribute to the pathogenesis of rheumatoid arthritis (Zhao *et al*, *Mol. Pharmacol.*, **2008**, *73*(2), 587-600). In one aspect, presented herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the treatment or prevention of rheumatoid arthritis in a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

30 In one aspect, LPA receptors (*e.g.* LPA₁) contribute to adipogenesis. (Simon *et al*, *J.Biol. Chem.*, 2005, vol. 280, no. 15, p.14656). In one aspect, presented herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the promotion of adipose tissue formation in a mammal comprising administering at least

once to the mammal an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

a. In Vitro Assays

5 The effectiveness of compounds of the present invention as LPA₁ inhibitors can be determined in an LPA₁ functional antagonist assay as follows:

Chinese hamster ovary cells overexpressing human LPA₁ were plated overnight (15,000 cells/well) in poly-D-lysine coated 384-well microplates (Greiner bio-one, Cat#781946) in DMEM/F12 medium (Gibco, Cat#11039). Following overnight culture, 10 cells were loaded with calcium indicator dye (AAT Bioquest Inc, Cat# 34601) for 30 minutes at 37 °C. The cells were then equilibrated to room temperature for 30 minutes before the assay. Test compounds solubilized in DMSO were transferred to 384 well non-binding surface plates (Corning, Cat# 3575) using the Labcyte Echo acoustic dispense and diluted with assay buffer [1X HBSS with calcium/magnesium (Gibco Cat# 14025-15 092), 20 mM HEPES (Gibco Cat# 15630-080) and 0.1% fatty acid free BSA (Sigma Cat# A9205)] to a final concentration of 0.5% DMSO. Diluted compounds were added to the cells by FDSS6000 (Hamamatsu) at final concentrations ranging from 0.08 nM to 5 μM. and were then incubated for 20 min at room temperature at which time LPA (Avanti Polar Lipids Cat#857130C) was added at final concentrations of 10 nM to stimulate the cells. 20 The compound IC₅₀ value was defined as the concentration of test compound which inhibited 50% of the calcium flux induced by LPA alone. IC₅₀ values were determined by fitting data to a 4-parameter logistic equation (GraphPad Prism, San Diego CA).

b. In Vivo Assays

25 LPA Challenge with plasma histamine evaluation.

Compound is dosed orally p.o. 2 hours to CD-1 female mice prior to the LPA challenge. The mice are then dosed via tail vein (IV) with 0.15 mL of LPA in 0.1%BSA/PBS (2 μg/μL). Exactly 2 minutes following the LPA challenge, the mice are euthanized by decapitation and the trunk blood is collected. These samples are collectively 30 centrifuged and individual 75 μL samples are frozen at -20°C until the time of the histamine assay.

The plasma histamine analysis was run by standard EIA (Enzyme Immunoassay) methods. Plasma samples were thawed and diluted 1:30 in 0.1% BSA in PBS. The EIA protocol for histamine analysis as outlined by the manufacturer was followed (Histamine EIA, Oxford Biomedical Research, EA#31).

5 The LPA used in the assay is formulated as follows: LPA (1-oleoyl-2-hydroxy-sn-glycero-3-phosphate (sodium salt), 857130P, Avanti Polar Lipids) is prepared in 0.1%BSA/PBS for total concentration of 2 $\mu\text{g}/\mu\text{L}$. 13 mg of LPA is weighed and 6.5 mL 0.1%BSA added, vortexed and sonicated for ~1 hour until a clear solution is achieved.

10 V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

In some embodiments, provided is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition
15 also contains at least one pharmaceutically acceptable inactive ingredient.

In some embodiments, provided is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable inactive ingredient. In one aspect, the pharmaceutical composition is formulated for intravenous
20 injection, subcutaneous injection, oral administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

25 In some embodiments, the pharmaceutical composition further comprises one or more additional therapeutically active agents selected from: corticosteroids (*e.g.*, dexamethasone or fluticasone), immunosuppressants (*e.g.*, tacrolimus & pimecrolimus), analgesics, anti-cancer agent, anti-inflammatories, chemokine receptor antagonists, bronchodilators, leukotriene receptor antagonists (*e.g.*, montelukast or zafirlukast),
30 leukotriene formation inhibitors, monoacylglycerol kinase inhibitors, phospholipase A₁ inhibitors, phospholipase A₂ inhibitors, and lysophospholipase D (lysoPLD) inhibitors, autotaxin inhibitors, decongestants, antihistamines (*e.g.*, loratidine), mucolytics,

anticholinergics, antitussives, expectorants, anti-infectives (*e.g.*, fusidic acid, particularly for treatment of atopic dermatitis), anti-fungals (*e.g.*, clotriazole, particularly for atopic dermatitis), anti-IgE antibody therapies (*e.g.*, omalizumab), β -2 adrenergic agonists (*e.g.*, albuterol or salmeterol), other PGD2 antagonists acting at other receptors such as DP
 5 antagonists, PDE4 inhibitors (*e.g.*, cilomilast), drugs that modulate cytokine production, *e.g.*, TACE inhibitors, drugs that modulate activity of Th2 cytokines IL-4 & IL-5 (*e.g.*, blocking monoclonal antibodies & soluble receptors), PPAR γ agonists (*e.g.*, rosiglitazone and pioglitazone), 5-lipoxygenase inhibitors (*e.g.*, zileuton).

In some embodiments, the pharmaceutical composition further comprises one or
 10 more additional anti-fibrotic agents selected from pirfenidone, nintedanib, thalidomide, carlumab, FG-3019, fresolimumab, interferon alpha, lecithinized superoxide dismutase, simtuzumab, tanzisertib, tralokinumab, hu3G9, AM-152, IFN-gamma-1b, IW-001, PRM-151, PXS-25, pentoxifylline/N-acetyl-cysteine, pentoxifylline/vitamin E, salbutamol sulfate, [Sar⁹,Met(O₂)¹¹]-Substance P, pentoxifylline, mercaptamine bitartrate,
 15 obeticholic acid, aramchol, GFT-505, eicosapentaenoic acid ethyl ester, metformin, metreleptin, muromonab-CD3, oltipraz, IMM-124-E, MK-4074, PX-102, RO-5093151.

In some embodiments, provided is a method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, to a human with a LPA-dependent or LPA-mediated disease or condition. In some embodiments, the human
 20 is already being administered one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the method further comprises administering one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the one or more additional therapeutically active agents
 25 other than a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, are selected from: corticosteroids (*e.g.*, dexamethasone or fluticasone), immunosuppressants (*e.g.*, tacrolimus & pimecrolimus), analgesics, anti-cancer agent, anti-inflammatories, chemokine receptor antagonists, bronchodilators, leukotriene
 30 receptor antagonists (*e.g.*, montelukast or zafirlukast), leukotriene formation inhibitors, monoacylglycerol kinase inhibitors, phospholipase A₁ inhibitors, phospholipase A₂ inhibitors, and lysophospholipase D (lysoPLD) inhibitors, autotaxin inhibitors,

decongestants, antihistamines (*e.g.*, loratidine), mucolytics, anticholinergics, antitussives, expectorants, anti-infectives (*e.g.*, fusidic acid, particularly for treatment of atopic dermatitis), anti-fungals (*e.g.*, clotriazole, particularly for atopic dermatitis), anti-IgE antibody therapies (*e.g.*, omalizumab), β -2 adrenergic agonists (*e.g.*, albuterol or salmeterol), other PGD2 antagonists acting at other receptors such as DP antagonists, PDE4 inhibitors (*e.g.*, cilomilast), drugs that modulate cytokine production, *e.g.* TACE inhibitors, drugs that modulate activity of Th2 cytokines IL-4 & IL-5 (*e.g.*, blocking monoclonal antibodies & soluble receptors), PPAR γ agonists (*e.g.*, rosiglitazone and pioglitazone), 5-lipoxygenase inhibitors (*e.g.*, zileuton).

10 In some embodiments, the one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, are other anti-fibrotic agents selected from pirfenidone, nintedanib, thalidomide, carlumab, FG-3019, fresolimumab, interferon alpha, lecithinized superoxide dismutase, simtuzumab, tanzisertib, tralokinumab, hu3G9, AM-152, IFN-gamma-1b, IW-001, PRM-151, PXS-25, pentoxifylline/N-acetyl-cysteine, pentoxifylline/vitamin E, salbutamol sulfate, [Sar⁹,Met(O₂)¹¹]-Substance P, pentoxifylline, mercaptamine bitartrate, obeticholic acid, aramchol, GFT-505, eicosapentyl ethyl ester, metformin, metreleptin, muromonab-CD3, oltipraz, IMM-124-E, MK-4074, PX-102, RO-5093151.

20 In some embodiments, the one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, are selected from ACE inhibitors, ramipril, AII antagonists, irbesartan, anti-arrhythmics, dronedarone, PPAR α activators, PPAR γ activators, pioglitazone, rosiglitazone, prostanoids, endothelin receptor antagonists, elastase inhibitors, calcium antagonists, beta blockers, diuretics, aldosterone receptor antagonists, eplerenone, renin inhibitors, rho kinase inhibitors, soluble guanylate cyclase (sGC) activators, sGC sensitizers, PDE inhibitors, PDE5 inhibitors, NO donors, digitalis drugs, ACE/NEP inhibitors, statins, bile acid reuptake inhibitors, PDGF antagonists, vasopressin antagonists, aquaretics, NHE1 inhibitors, Factor Xa antagonists, Factor XIIIa antagonists, anticoagulants, anti-thrombotics, platelet inhibitors, profibrotics, thrombin-activatable fibrinolysis inhibitors (TAFI), PAI-1 inhibitors, coumarins, heparins, thromboxane antagonists, serotonin antagonists, COX inhibitors, aspirin, therapeutic antibodies, GPIIb/IIIa antagonists, ER antagonists, SERMs, tyrosine kinase inhibitors, RAF kinase

inhibitors, p38 MAPK inhibitors, pirfenidone, multi-kinase inhibitors, nintedanib, sorafenib.

In some embodiments, the one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, are selected from Gremlin-1 mAb, PA1-1 mAb, Promedior (PRM-151; 5 recombinant human Pentraxin-2); FGF21, TGF β antagonists, α v β 6 & α v β pan-antagonists; FAK inhibitors, TG2 inhibitors, LOXL2 inhibitors, NOX4 inhibitors, MGAT2 inhibitors, GPR120 agonists.

Pharmaceutical formulations described herein are administrable to a subject in a 10 variety of ways by multiple administration routes, including but not limited to, oral, parenteral (*e.g.*, intravenous, subcutaneous, intramuscular), intranasal, buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate 15 release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

In some embodiments, the compound of Formula (I), or a pharmaceutically 20 acceptable salt or solvate thereof, is administered orally.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is administered topically. In such embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is 25 formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. In one aspect, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is administered topically to the skin.

30 In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is administered by inhalation. In one embodiment, the compound

of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is administered by inhalation that directly targets the pulmonary system.

In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is formulated for intranasal administration. Such formulations
5 include nasal sprays, nasal mists, and the like.

In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is formulated as eye drops.

In another aspect is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a
10 disease, disorder or conditions in which the activity of at least one LPA receptor contributes to the pathology and/or symptoms of the disease or condition. In one embodiment of this aspect, the LPA is selected from LPA₁, LPA₂, LPA₃, LPA₄, LPA₅ and LPA₆. In one aspect, the LPA receptor is LPA₁. In one aspect, the disease or condition is any of the diseases or conditions specified herein.

15 In any of the aforementioned aspects are further embodiments in which: (a) the effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is systemically administered to the mammal; and/or (b) the effective amount of the compound is administered orally to the mammal; and/or (c) the effective amount of the compound is intravenously administered to the mammal; and/or (d) the
20 effective amount of the compound is administered by inhalation; and/or (e) the effective amount of the compound is administered by nasal administration; or and/or (f) the effective amount of the compound is administered by injection to the mammal; and/or (g) the effective amount of the compound is administered topically to the mammal; and/or (h) the effective amount of the compound is administered by ophthalmic administration;
25 and/or (i) the effective amount of the compound is administered rectally to the mammal; and/or (j) the effective amount is administered non-systemically or locally to the mammal.

In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments
30 in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) 5 the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the 10 drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

Also provided is a method of inhibiting the physiological activity of LPA in a mammal comprising administering a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof to the mammal in 15 need thereof.

In one aspect, provided is a medicament for treating a LPA-dependent or LPA-mediated disease or condition in a mammal comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In some cases disclosed herein is the use of a compound of Formula (I), or a 20 pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a LPA-dependent or LPA-mediated disease or condition.

In some cases disclosed herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the treatment or prevention of a LPA-dependent or LPA-mediated disease or condition.

25 In one aspect, is a method for treating or preventing a LPA-dependent or LPA-mediated disease or condition in a mammal comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, LPA-dependent or LPA-mediated diseases or conditions include, 30 but are not limited to, fibrosis of organs or tissues, scarring, liver diseases, dermatological conditions, cancer, cardiovascular disease, respiratory diseases or conditions, inflammatory disease, gastrointestinal tract disease, renal disease, urinary tract-associated

disease, inflammatory disease of lower urinary tract, dysuria, frequent urination, pancreas disease, arterial obstruction, cerebral infarction, cerebral hemorrhage, pain, peripheral neuropathy, and fibromyalgia.

In one aspect, the LPA-dependent or LPA-mediated disease or condition is a
5 respiratory disease or condition. In some embodiments, the respiratory disease or
condition is asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis,
pulmonary arterial hypertension or acute respiratory distress syndrome.

In some embodiments, the LPA-dependent or LPA-mediated disease or condition
is selected from idiopathic pulmonary fibrosis; other diffuse parenchymal lung diseases of
10 different etiologies including iatrogenic drug-induced fibrosis, occupational and/or
environmental induced fibrosis, granulomatous diseases (sarcoidosis, hypersensitivity
pneumonia), collagen vascular disease, alveolar proteinosis, langerhans cell
granulomatosis, lymphangiomyomatosis, inherited diseases (Hermansky-Pudlak
Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial
15 interstitial lung disease); radiation induced fibrosis; chronic obstructive pulmonary
disease (COPD); scleroderma; bleomycin induced pulmonary fibrosis; chronic asthma;
silicosis; asbestos induced pulmonary fibrosis; acute respiratory distress syndrome
(ARDS); kidney fibrosis; tubulointerstitium fibrosis; glomerular nephritis; focal
segmental glomerular sclerosis; IgA nephropathy; hypertension; Alport; gut fibrosis; liver
20 fibrosis; cirrhosis; alcohol induced liver fibrosis; toxic/drug induced liver fibrosis;
hemochromatosis; nonalcoholic steatohepatitis (NASH); biliary duct injury; primary
biliary cirrhosis; infection induced liver fibrosis; viral induced liver fibrosis; and
autoimmune hepatitis; corneal scarring; hypertrophic scarring; Duputren disease, keloids,
cutaneous fibrosis; cutaneous scleroderma; spinal cord injury/fibrosis; myelofibrosis;
25 vascular restenosis; atherosclerosis; arteriosclerosis; Wegener's granulomatosis;
Peyronie's disease, chronic lymphocytic leukemia, tumor metastasis, transplant organ
rejection, endometriosis, neonatal respiratory distress syndrome and neuropathic pain.

In one aspect, the LPA-dependent or LPA-mediated disease or condition is
described herein.

30 In one aspect, provided is a method for the treatment or prevention of organ
fibrosis in a mammal comprising administering a therapeutically effective amount of a

compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof to a mammal in need thereof.

In one aspect, the organ fibrosis comprises lung fibrosis, renal fibrosis, or hepatic fibrosis.

5 In one aspect, provided is a method of improving lung function in a mammal comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof to the mammal in need thereof. In one aspect, the mammal has been diagnosed as having lung fibrosis.

10 In one aspect, compounds disclosed herein are used to treat idiopathic pulmonary fibrosis (usual interstitial pneumonia) in a mammal.

In some embodiments, compounds disclosed herein are used to treat diffuse parenchymal interstitial lung diseases in mammal: iatrogenic drug induced, occupational/environmental (Farmer lung), granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease (scleroderma and others), alveolar
15 proteinosis, langerhans cell granulomatosis, lymphangiomyomatosis, Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease.

In some embodiments, compounds disclosed herein are used to treat post-transplant fibrosis associated with chronic rejection in a mammal: Bronchiolitis obliterans
20 for lung transplant.

In some embodiments, compounds disclosed herein are used to treat cutaneous fibrosis in a mammal: cutaneous scleroderma, Dupuytren disease, keloids.

In one aspect, compounds disclosed herein are used to treat hepatic fibrosis with or without cirrhosis in a mammal: toxic/drug induced (hemochromatosis), alcoholic liver
25 disease, viral hepatitis (hepatitis B virus, hepatitis C virus, HCV), nonalcoholic liver disease (NAFLD, NASH), metabolic and auto-immune disease.

In one aspect, compounds disclosed herein are used to treat renal fibrosis in a mammal: tubulointerstitium fibrosis, glomerular sclerosis.

In any of the aforementioned aspects involving the treatment of LPA dependent
30 diseases or conditions are further embodiments comprising administering at least one additional agent in addition to the administration of a compound having the structure of

Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In various embodiments, each agent is administered in any order, including simultaneously.

In any of the embodiments disclosed herein, the mammal is a human.

In some embodiments, compounds provided herein are administered to a human.

5 In some embodiments, compounds provided herein are orally administered.

In some embodiments, compounds provided herein are used as antagonists of at least one LPA receptor. In some embodiments, compounds provided herein are used for inhibiting the activity of at least one LPA receptor or for the treatment of a disease or condition that would benefit from inhibition of the activity of at least one LPA receptor.

10 In one aspect, the LPA receptor is LPA₁.

In other embodiments, compounds provided herein are used for the formulation of a medicament for the inhibition of LPA₁ activity.

Articles of manufacture, which include packaging material, a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, within the packaging
15 material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, tautomers, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for inhibiting the activity of at least one LPA receptor, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition
20 that would benefit from inhibition of the activity of at least one LPA receptor, are provided.

VI. GENERAL SYNTHESIS INCLUDING SCHEMES

The compounds of the present invention can be prepared in a number of ways
25 known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture
30 appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations

proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

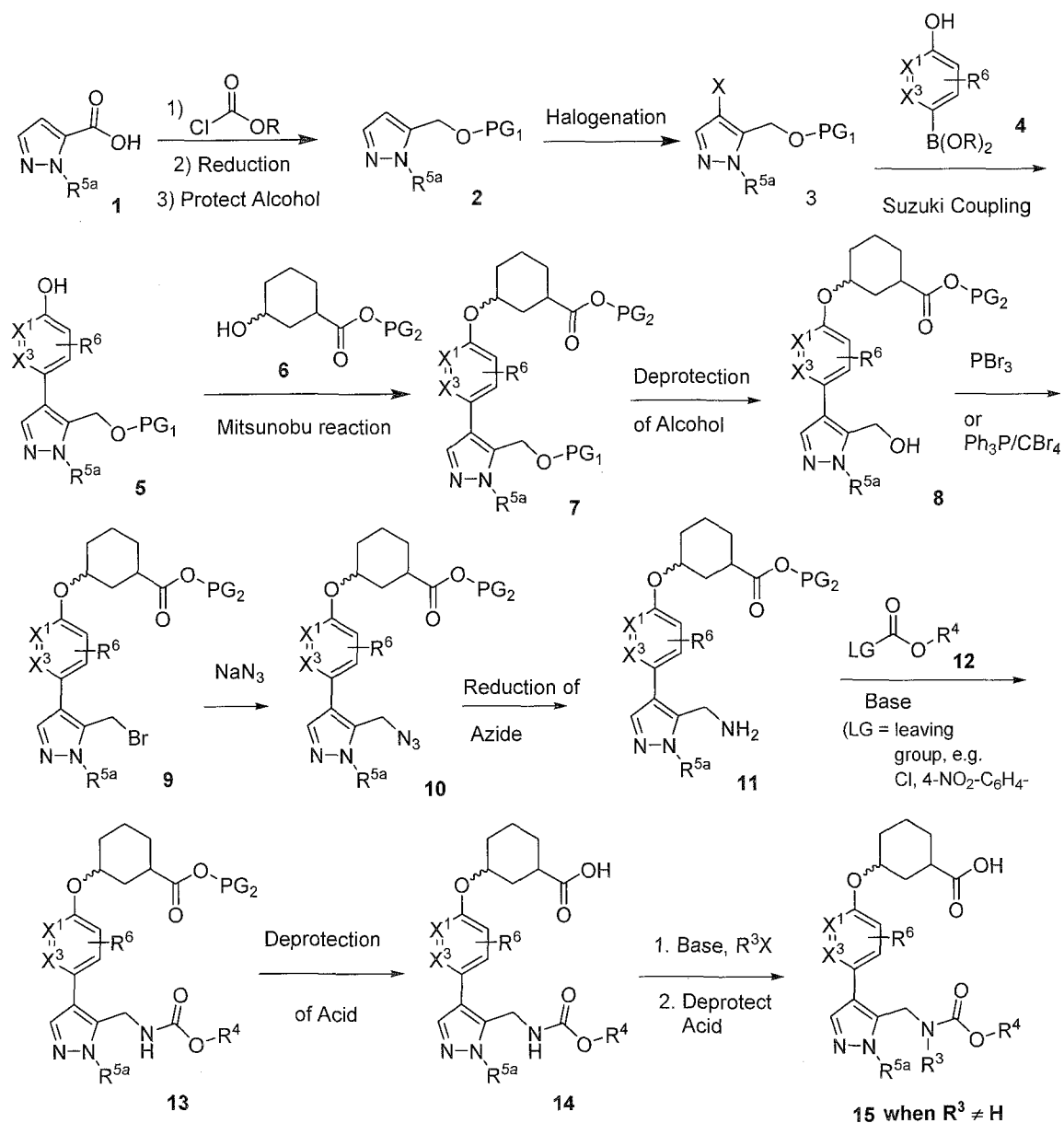
It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al., (*Protective Groups in Organic Synthesis*, Fourth Edition, Wiley-Interscience (2006)).

The compounds of Formula (I) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear herein after and in the working examples. Protection and deprotection in the processes below may be carried out by procedures generally known in the art (see, for example, Wuts, P.G.M., *Greene's Protective Groups in Organic Synthesis*, 5th Edition, Wiley (2014)). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. et al., Eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*, Pergamon Press, New York, NY (1991); Smith, M.B. et al., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 7th Edition, Wiley, New York, NY (2013); Katritzky, A.R. et al., Eds., *Comprehensive Organic Functional Group Transformations II*, 2nd Edition, Elsevier Science Inc., Tarrytown, NY (2004); Larock, R.C., *Comprehensive Organic Transformations*, 2nd Edition, Wiley-VCH, New York, NY (1999), and references therein.

Scheme 1 describes the synthesis of N-carbamoyl pyrazole-aryloxy cyclohexyl acids 14 and 15. A pyrazole 5-carboxylic acid 1 is reduced (e.g. by a 2 step, 1-pot reaction via reaction with an alkyl chloroformate followed by low-temperature reduction with NaBH₄, or directly with diborane) to the corresponding pyrazole alcohol, which is then protected to give pyrazole intermediate 2. Halogenation of pyrazole 2 occurs preferentially at the 4-pyrazole position to give protected halopyrazole alcohol 3, which is then subjected to a Suzuki-Miyaura cross-coupling reaction with an appropriately substituted 4-hydroxy-aryl/heteroaryl boronate 4 to provide the corresponding 4-hydroxy-

aryl(heteroaryl)-pyrazole 5. Reaction of phenol/ hydroxyheteroarene 5 with a 3-hydroxy cyclohexyl ester 6 under Mitsunobu reaction conditions (Kumara Swamy, K. C., *Chem. Rev.*, **2009**, *109*, 2551-2651) furnishes the corresponding pyrazole cycloalkyl ether ester 7. Deprotection of the hydroxymethylpyrazole 7 provides the cyclohexyl ester pyrazole alcohol 8. Pyrazole alcohol 8 is then reacted with PBr₃ (or another mild brominating agent such as CBr₄/Ph₃P) to give the corresponding bromide 9. Displacement of pyrazole bromide 9 with NaN₃ (or other azide equivalent reagents) gives pyrazole azide 10 which undergoes reduction (e.g. Staudinger reduction with Ph₃P/water) to afford pyrazole amine 11. Pyrazole amine 11 is reacted with an appropriate acylating agent 12 (e.g. chloroformate or 4-nitrophenylcarbonate) to provide the cyclohexyl pyrazole N-H carbamate ester 13. Cyclohexyl ester 13 is deprotected to give the NH-carbamoyl methyl pyrazole-aryloxy cyclohexyl acids 14. The cyclohexyl pyrazole NH-carbamate ester 13, upon treatment with an appropriate base (e.g. NaH) followed by reaction with an alkyl halide (R³X) gives the pyrazole N,N-disubstituted carbamate cyclohexyl ester, which is then deprotected to provide the N,N-dialkyl-carbamoyl pyrazole-aryloxy cyclohexyl acids 15.

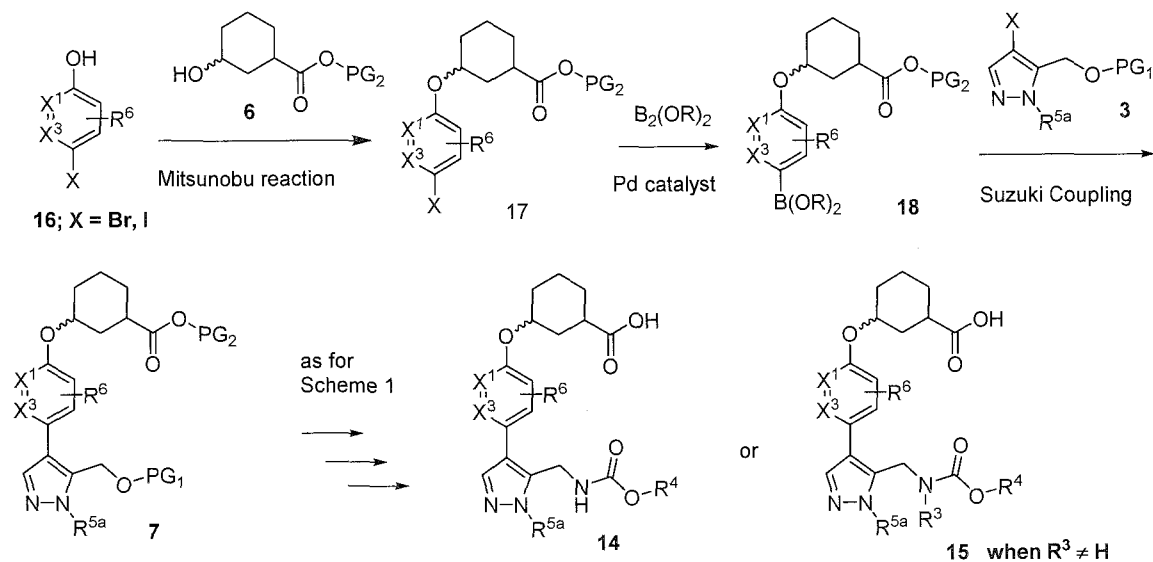
Scheme 1



Scheme 2 describes an alternative synthesis of N-carbamoyl pyrazole-aryloxy cyclohexyl acids 14 and 15. A 4-hydroxy-aryl/heteroaryl halide 16 is reacted with a 3-hydroxy cyclohexyl ester 6 under Mitsunobu reaction conditions to furnish the corresponding 4-halo-aryl-oxy-cycloalkyl ester 17. Borylation (e.g. with pinacol diboronate in the presence of an appropriate palladium catalyst, ref. Ishiyama, T. et al, *J. Org. Chem.* **1995**, *60*, 7508-7510) of aryl/heteroaryl halide 17 provides the aryl/heteroaryl boronate (which can be converted to the corresponding boronic acid) 18, which is then subjected to a Suzuki-Miyaura coupling with halo-pyrazole protected alcohol 3 to furnish

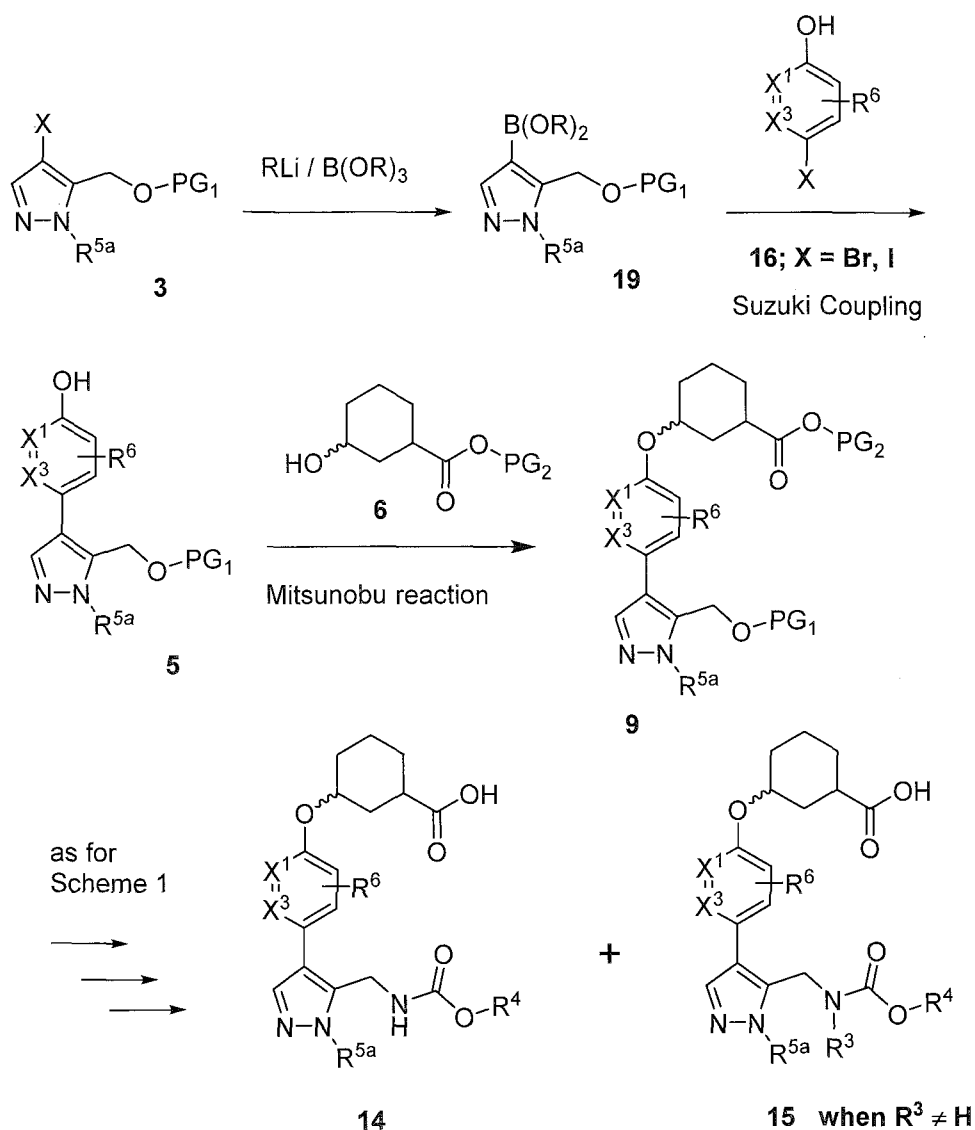
the corresponding pyrazole-aryl/heteroaryl oxycycloalkyl ester 7. Cyclohexyl ester-pyrazole ether 7 is then converted to the N-carbamoyl pyrazole-aryloxy cyclohexyl acids 14 and 15 by the same synthetic sequence as described in Scheme 1.

5 Scheme 2



Scheme 3 describes another alternative synthetic route to N-carbamoyl pyrazole-aryloxy cyclohexyl acids 14 and 15. An appropriately protected halo-pyrazole alcohol 3 is metalated (e.g. with n-BuLi) and reacted with a borylating agent $B(OR)_3$ to provide the pyrazole boronate 19. This pyrazole boronate 19 is then subjected to a Suzuki-Miyaura coupling reaction with an appropriate 4-hydroxy aryl/heteroaryl halide 16 to directly provide the 4-haloaryl/heteroaryl-pyrazole 5. Reaction of phenol/hydroxyheteroarene 5 with a 3-hydroxy cyclohexyl ester 6 under Mitsunobu reaction conditions furnishes the corresponding pyrazole oxycycloalkyl ester 7, which is then carried forward to the N-carbamoyl pyrazole-aryloxy cyclohexyl acids 14 and 15 by the same synthetic sequence as described in Scheme 1.

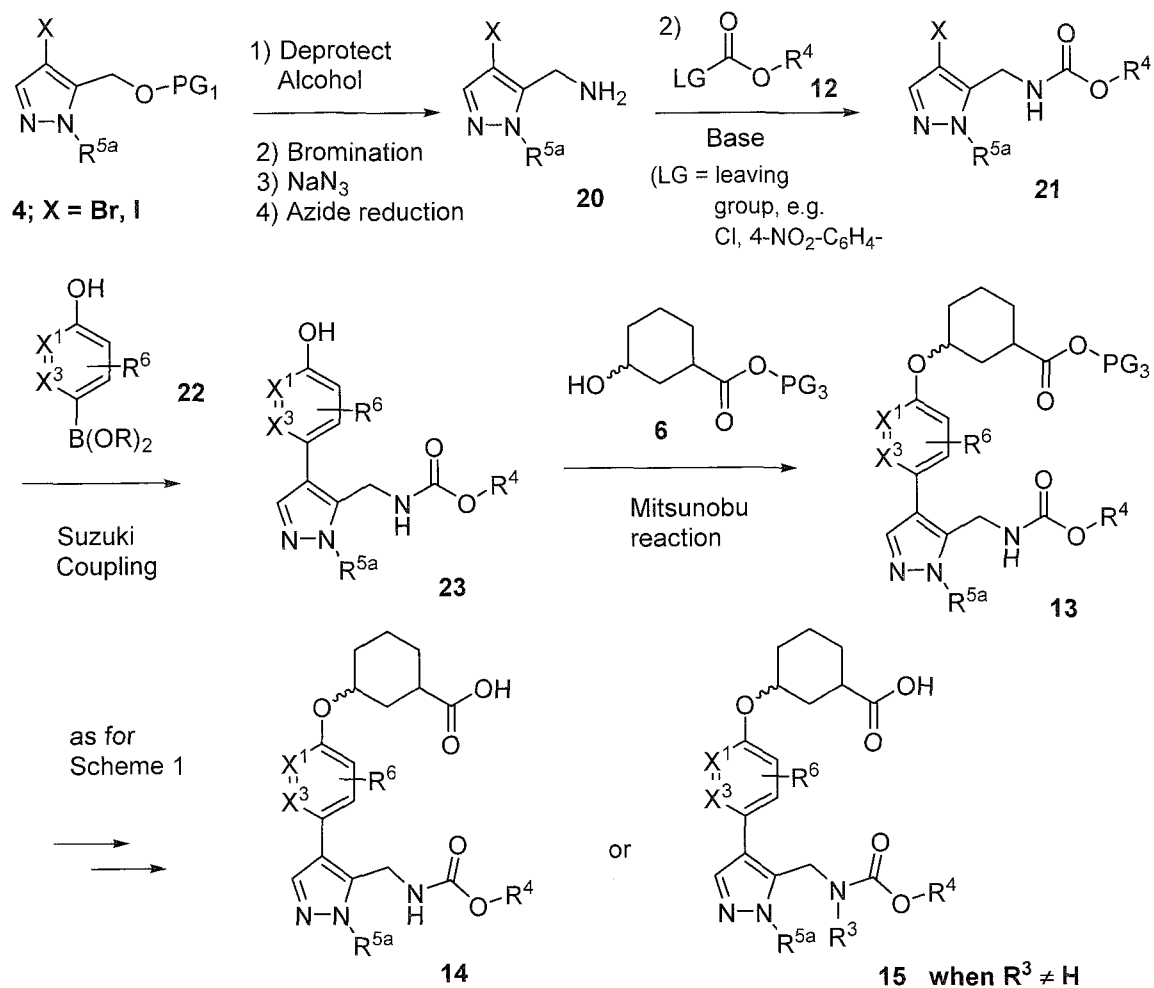
Scheme 3



Scheme 4 describes the synthesis of N-carbamoyl pyrazole-aryloxy cyclohexyl acids 14 and 15 via a synthetic route that involves the initial preparation of a fully elaborated pyrazole N-carbamate intermediate. Pyrazole alcohol 18 is deprotected, then converted to the corresponding pyrazole amine 20 using the same 3-step sequence as described in Scheme 1 (from alcohol 8 to amine 11, via conversion to the bromide with PBr_3 or $\text{CBr}_4/\text{Ph}_3\text{P}$, bromide displacement with NaN_3 , and azide reduction with $\text{Ph}_3\text{P}/\text{water}$). Pyrazole amine 20 is reacted with an appropriate acylating agent 12 (e.g. chloroformate or 4-nitrophenylcarbonate) to provide the pyrazole N-H carbamate 21. The halo-pyrazole carbamate 21 is then subjected to a Suzuki-Miyaura cross-coupling reaction with an appropriately substituted 4-hydroxy-aryl/heteroaryl boronate/boronic acid 22 to

provide the corresponding hydroxyaryl/hydroxyheteroaryl pyrazole carbamate 23, which is then subjected to a Mitsunobu reaction with a 3-hydroxy cyclohexyl ester 6 to furnish the corresponding pyrazole oxycycloalkyl ester 13. The pyrazole N-carbamate cycloalkyl ester 13 is then carried forward to the N-carbamoyl pyrazole-aryloxy cyclohexyl acids 15 and 16 by the same synthetic sequence as described in Scheme 1.

Scheme 4

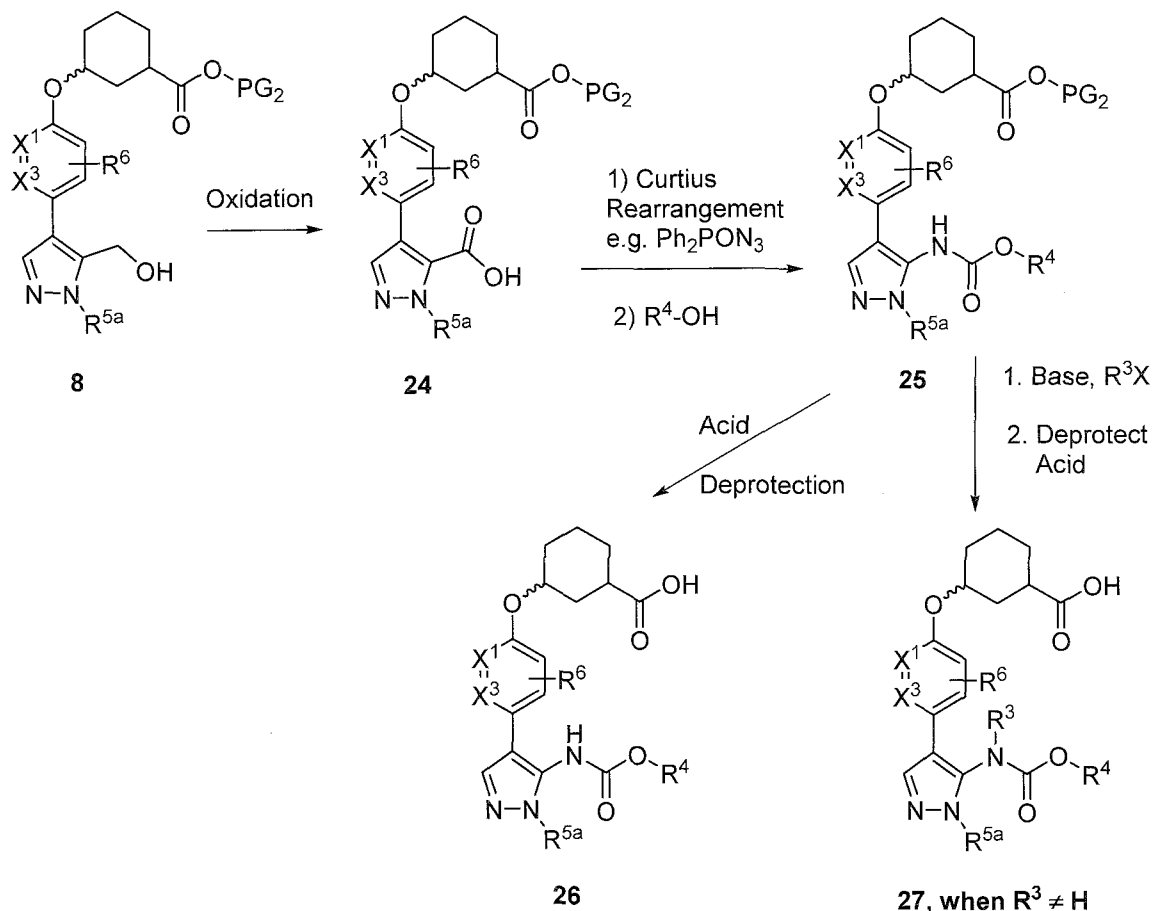


10 Scheme 5 describes the synthesis of pyrazole N-linked carbamate cyclohexyl acids 26 and 27. The cyclohexyl ether pyrazole-alcohol 8 is oxidized to the pyrazole carboxylic acid 24 (e.g. directly to the acid with pyridinium dichromate or via a 2-step procedure via the aldehyde [Swern oxidation or Dess-Martin periodinane followed by NaClO₂ oxidation to the acid, e.g. Lindgren, B. O., *Acta Chem. Scand.* **1973**, 27, 888]).

15 Curtius rearrangement of pyrazole acid 24 in the presence of an alcohol R⁴-OH furnishes

the pyrazole NH-carbamate 25. Deprotection of the pyrazole NH-carbamate cyclohexyl ester 25 gives the pyrazole NH-carbamate cyclohexyl acids 26. Alternatively, pyrazole NH-carbamate cyclohexyl ester 25 is deprotonated with an appropriate base and reacted (as described in Scheme 1) with an alkyl R³-halide to provide the pyrazole N,N-dialkyl carbamate acids 26.

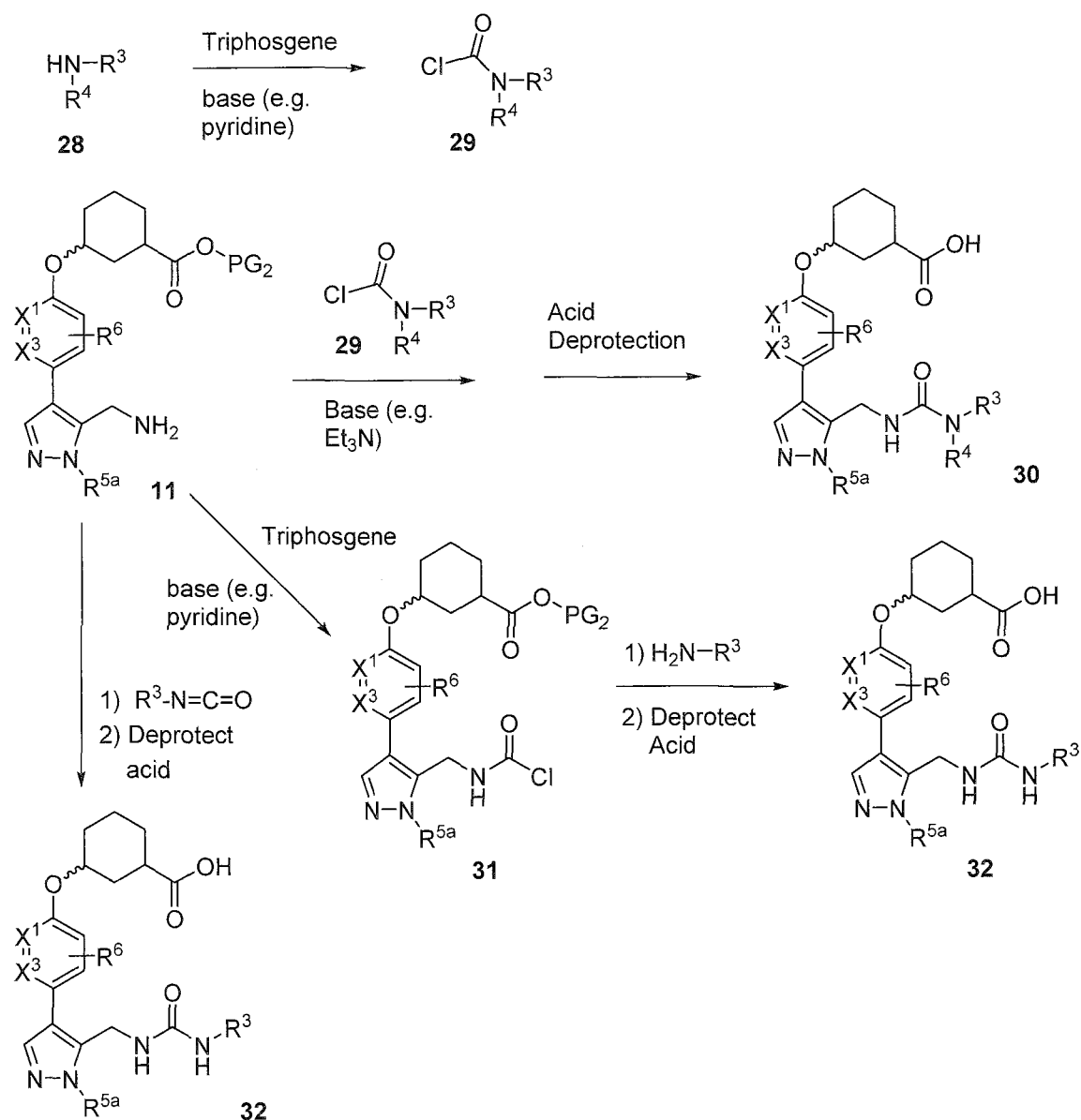
Scheme 5



Scheme 6 describes the synthesis of N-ureido-pyrazole-aryloxy cyclohexyl acids 30 and 32. Pyrazole amine 12 undergoes reaction with a carbamoyl chloride 29 (prepared, e.g., from the reaction of a secondary amine 28 with triphosgene) to give the corresponding ureido-pyrazole cyclohexyl ester, which is then deprotected to provide the ureido-isoxazole cyclohexyl acids 30. In a complementary synthetic route, isoxazole amine 12 undergoes reaction with triphosgene to give the isoxazole carbamoyl chloride 31, which is reacted with a primary amine R³-NH₂ (or with a secondary amine 28) to give (after ester deprotection) the corresponding N-alkyl-ureido-pyrazole aryloxy cyclohexyl

acids 32 (with secondary amines the products are the N,N' -dialkyl ureido-pyrazole acids 30). Alternatively, the pyrazole amine 11 is reacted with isocyanates R^3NCO to give, after ester deprotection, N -alkyl-ureido-pyrazole cyclohexyl acids 32.

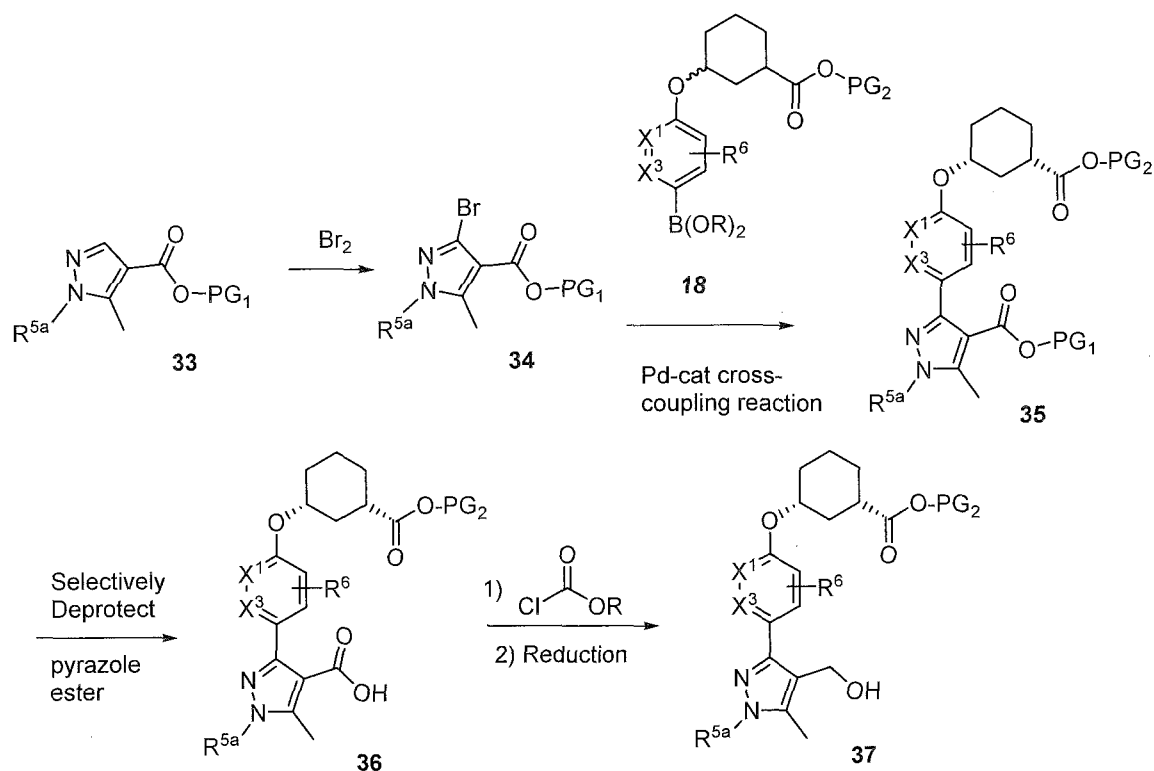
5 Scheme 6

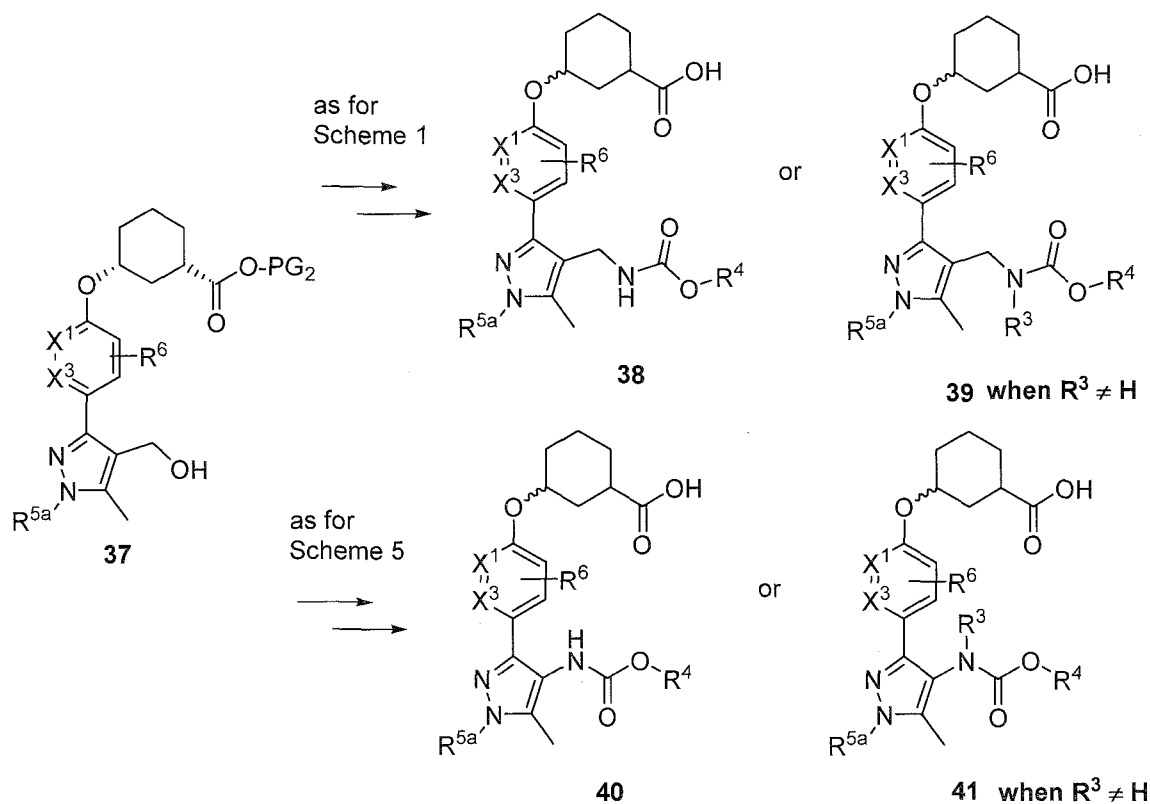


Scheme 7 describes the synthesis of N -carbamoyl pyrazole-aryloxy cyclohexyl acids 38 and 39. An appropriately protected 1,5-dialkyl-1H-pyrazole-4-carboxylic acid ester 33 is brominated to give bromo-pyrazole 34. The bromopyrazole 34 is then subjected to a Suzuki-Miyaura coupling reaction with the aryl/heteroaryl boronate 18 (or

the corresponding boronic acid), to furnish the corresponding pyrazole-aryl/heteroaryl
 oxycycloalkyl ester 35. The pyrazole ester of 35 is selectively deprotected to the
 corresponding pyrazole carboxylic acid 36, which then undergoes reduction (e.g. by a 2
 step, 1-pot reaction via reaction with an alkyl chloroformate followed by low-temperature
 5 reduction with NaBH₄, or directly with diborane as in Scheme 1) to the corresponding
 pyrazole alcohol 37. Cyclohexyl ester-pyrazole alcohol 37 is then converted to the
 pyrazole N-carbamoyl cyclohexyl acids 38 and 39 by the same synthetic sequence as
 described in Scheme 1. Alternatively, cyclohexyl ester-pyrazole alcohol 37 is also then
 converted to the pyrazole N-carbamate aryloxy cyclohexyl acids 40 and 41 by the same
 10 synthetic sequence as described in Scheme 5.

Scheme 7





VII. EXAMPLES

The following Examples are offered as illustrative, as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the schemes and other methods disclosed herein or may be prepared using the same.

As appropriate, reactions were conducted under an atmosphere of dry nitrogen (or argon). For anhydrous reactions, DRISOLV® solvents from EM were employed. For other reactions, reagent grade or HPLC grade solvents were utilized. Unless otherwise stated, all commercially obtained reagents were used as received.

Microwave reactions were carried out using a 400W Biotage Initiator instrument in microwave reaction vessels under microwave (2.5 GHz) irradiation.

HPLC/MS and preparatory/analytical HPLC methods employed in characterization or purification of examples

NMR (nuclear magnetic resonance) spectra were typically obtained on Bruker or JEOL 400 MHz and 500 MHz instruments in the indicated solvents. All chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. ¹H NMR spectral data are typically reported as follows: chemical shift, 5 multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet, app = apparent), coupling constants (Hz), and integration.

In the examples where ¹H NMR spectra were collected in d₆-DMSO, a water-suppression sequence is often utilized. This sequence effectively suppresses the water 10 signal and any proton peaks in the same region usually between 3.30-3.65 ppm which will affect the overall proton integration.

The term HPLC refers to a Shimadzu high performance liquid chromatography instrument with one of following methods:

15 HPLC-1: Sunfire C18 column (4.6 × 150 mm) 3.5 μm, gradient from 10 to 100% B:A for 12 min, then 3 min hold at 100% B.

Mobile phase A: 0.05% TFA in water:CH₃CN (95:5)

Mobile phase B: 0.05% TFA in CH₃CN:water (95:5)

TFA Buffer pH = 2.5; Flow rate: 1 mL/ min; Wavelength: 254 nm, 220 nm.

20

HPLC-2: XBridge Phenyl (4.6 × 150 mm) 3.5 μm, gradient from 10 to 100% B:A for 12 min, then 3 min hold at 100% B.

Mobile phase A: 0.05% TFA in water:CH₃CN (95:5)

Mobile phase B: 0.05% TFA in CH₃CN:water (95:5)

25 TFA Buffer pH = 2.5; Flow rate: 1 mL/ min; Wavelength: 254 nm, 220 nm.

HPLC-3: Chiralpak AD-H, 4.6 × 250 mm, 5 μm.

Mobile Phase: 30% EtOH-heptane (1:1) / 70% CO₂

Flow rate = 40 mL/min, 100 Bar, 35 °C; Wavelength: 220 nm

30

HPLC-4: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7-μm particles;

Mobile Phase A: 5:95 CH₃CN:water with 10 mM NH₄OAc;

Mobile Phase B: 95:5 CH₃CN:water with 10 mM NH₄OAc;

Temperature: 50 °C; Gradient: 0-100% B over 3 min, then a 0.75-min hold at 100% B;

Flow: 1.11 mL/min; Detection: UV at 220 nm.

5 HPLC-5: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7- μ m particles;

Mobile Phase A: 5:95 CH₃CN:water with 0.1% TFA;

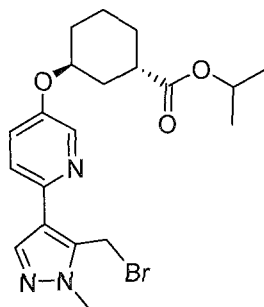
Mobile Phase B: 95:5 CH₃CN:water with 0.1% TFA;

Temperature: 50 °C; Gradient: 0-100% B over 3 min, then a 0.75-min hold at 100%

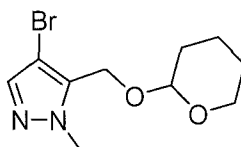
B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

10

Intermediate 1. Isopropyl trans-3-((6-(5-(bromomethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylate



15 Intermediate 1A. 4-bromo-1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazole



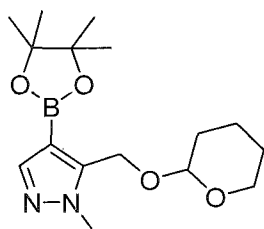
pTsOH.H₂O (0.050 g, 0.262 mmol) was added to a solution of (4-bromo-1-methyl-1H-pyrazol-5-yl)methanol (1.0 g, 5.2 mmol) and 3,4-dihydro-2H-pyran (1.32 g, 15.7 mmol) in DCM (10 mL) at 0 °C. The reaction was allowed to warm to RT and stirred overnight at RT. The reaction was cooled to 0 °C and neutralized with satd aq. NaHCO₃ to pH 7. The mixture was partitioned between DCM (10 mL) and water (10 mL), and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; EtOAc/hexanes) to provide title compound (1.40 g, 5.09 mmol,

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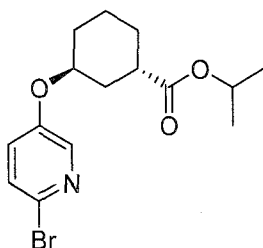
97 % yield) as a colorless oil. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.41 (s, 1H), 4.72 (d, J = 12.9 Hz, 1H), 4.65 (dd, J = 4.1, 3.0 Hz, 1H), 4.58 (d, J = 12.9 Hz, 1H), 3.93 (s, 3H), 3.88 (ddd, J = 11.6, 8.3, 3.1 Hz, 1H), 3.57 (dddd, J = 11.0, 5.0, 3.9, 1.4 Hz, 1H), 3.49 (d, J = 5.5 Hz, 2H), 1.85 – 1.75 (m, 1H), 1.75 – 1.66 (m, 1H), 1.66 – 1.48 (m, 4H). LCMS, $[\text{M}+\text{H}]^+ = 275.1$.

Intermediate 1B. 1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



10 A mixture of Intermediate 1A (469 mg, 1.71 mmol), KOAc (502 mg, 5.11 mmol), bis(pinacolato) diboron (649 mg, 2.56 mmol) in 1,4 dioxane (10 ml) was degassed with N_2 for 5 min. $\text{PdCl}_2(\text{dppf})$ (125 mg, 0.170 mmol) was added and the reaction was degassed again with N_2 for 5 min. The reaction vessel was sealed and heated at 85 °C for 10 h, then was cooled to RT. The mixture was partitioned between EtOAc (10 mL) and
15 water (10 mL), the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (MgSO_4) and concentrated in vacuo to afford the crude title compound (717 mg, 0.890 mmol, 52.2 % yield) as a yellow colorless oil. LCMS, $[\text{M}+\text{H}]^+ = 323.1$.

20 Intermediate 1C. isopropyl trans-3-(((6-bromopyridin-3-yl)oxy)cyclohexane-1-carboxylate

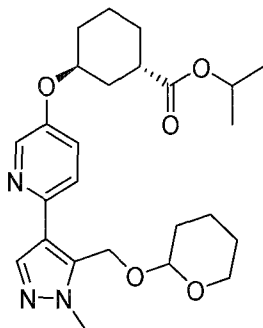


To a mixture of 6-bromopyridin-3-ol (300 mg, 1.72 mmol), (\pm)-cis-isopropyl 3-hydroxycyclo-hexane carboxylate (353 mg, 1.90 mmol), Et_3N (0.264 mL, 1.90 mmol) and Ph_3P (497 mg, 1.90 mmol) in THF (2 mL) at 0 °C was added DIAD (0.369 mL, 1.90
25 mmol) dropwise over 15 min. The reaction was stirred overnight at RT, then was

partitioned between EtOAc (5 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄) and concentrated in vacuo. The crude product was chromatographed (SiO₂; EtOAc/hexanes) to provide the title compound (255 mg, 0.745 mmol, 43.2 %

5 yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.07 (d, *J* = 3.2 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 8.7, 3.1 Hz, 1H), 5.02 (hept, *J* = 6.3 Hz, 1H), 4.61 (dq, *J* = 8.7, 5.3, 4.2 Hz, 1H), 2.76 (tt, *J* = 9.0, 4.4 Hz, 1H), 2.03 – 1.51 (m, 8H), 1.24 (dd, *J* = 6.3, 1.9 Hz, 6H). LCMS, [M+H]⁺ = 342.

10 Intermediate 1D. Isopropyl trans-3-(((6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate

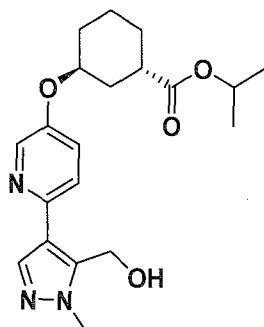


To the solution of Intermediate 1B (717 mg, 0.891 mmol) in 1,4-dioxane (2 mL) was added 1C (254 mg, 0.742 mmol), and K₂HPO₄ (388 mg, 2.23 mmol), 2nd generation XPhos precatalyst (29 mg, 0.037 mmol) and water (2 mL). The mixture was evacuated in vacuo and recharged with Ar (3X). The mixture was stirred at 60 °C for 24 h, then cooled to RT and stirred at RT for 24 h. The mixture was extracted with EtOAc (3 x 5 mL), dried (MgSO₄) and concentrated in vacuo to afford the crude product. The crude material was chromatographed (12 g SiO₂, continuous gradient from 0 to 100% EtOAc in hexanes in 12 min) to afford the title compound (212 mg, 0.417 mmol, 56.2 % yield) as a slightly yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.30 (d, *J* = 2.9 Hz, 1H), 7.76 (s, 1H), 7.46 – 7.39 (m, 1H), 7.28 – 7.21 (m, 1H), 5.08 – 4.94 (m, 3H), 4.72 (dd, *J* = 4.5, 3.0 Hz, 1H), 4.65 (tq, *J* = 5.5, 2.8 Hz, 1H), 3.97 (s, 3H), 3.88 (ddd, *J* = 11.3, 7.9, 3.2 Hz, 1H), 3.56 – 3.45 (m, 1H), 2.80 (tt, *J* = 9.8, 4.1 Hz, 1H), 2.09 – 1.48 (m, 14H), 1.24 (dd, *J* = 6.3, 1.8 Hz, 6H). LCMS, [M+H]⁺ = 458.1.

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Intermediate 1E. isopropyl trans-3-(((6-(5-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



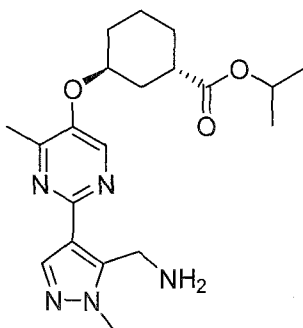
To a solution of Intermediate 1D (212 mg, 0.463 mmol) in MeOH (5 mL) was
 5 added PPTS (12 mg, 0.046 mmol). The mixture was heated at 60°C for 4 h, then was
 cooled to RT, quenched with satd aq. NaHCO₃ (2 mL) and concentrated in vacuo to
 remove the MeOH. The residue was extracted with EtOAc (3 x 5 mL). The combined
 organic extracts were dried (MgSO₄) and concentrated in vacuo. The crude product was
 chromatographed (4 g SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes, 12
 10 min) to afford the title compound (75 mg, 0.201 mmol, 43.3 % yield) as a colorless oil.
¹H NMR (500 MHz, CDCl₃) δ 8.15 (d, *J* = 2.9 Hz, 1H), 7.66 (s, 1H), 7.43 (d, *J* = 8.8 Hz,
 1H), 7.26 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.93 (s, 1H), 4.95 (hept, *J* = 6.2 Hz, 1H), 4.65 (s, 2H),
 4.58 (dq, *J* = 5.8, 2.8 Hz, 1H), 3.85 (3, 3H), 2.72 (tt, *J* = 9.0, 4.3 Hz, 1H), 1.99 – 1.46 (m,
 8H), 1.17 (dd, *J* = 6.3, 2.3 Hz, 6H). LCMS, [M+H]⁺ = 374.2.

15

Intermediate 1

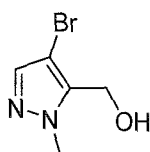
PBr₃ (0.040 mL, 0.426 mmol) was added to a solution of Intermediate 1E (53 mg,
 0.142 mmol) in DME (1.5 mL) at 0 °C. The reaction was stirred overnight at RT, then
 was cooled to 0 °C and neutralized with satd aq. NaHCO₃ to pH 7. The mixture was
 20 partitioned between DCM (5 mL) and water (3 mL) and the aqueous layer was extracted
 with DCM (3 x 3 mL). The combined organics extracts were dried (MgSO₄) and
 concentrated in vacuo. The residue was chromatographed (SiO₂; EtOAc/hexanes) to
 provide the title compound (55 mg, 0.126 mmol, 89 % yield) as a white solid. ¹H NMR
 (500 MHz, CDCl₃) δ 8.34 (d, *J* = 2.8 Hz, 1H), 7.74 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.32
 25 – 7.24 (m, 1H), 5.11 (s, 2H), 5.04 (p, *J* = 6.2 Hz, 1H), 4.68 (tt, *J* = 5.5, 3.0 Hz, 1H), 3.96
 (s, 3H), 2.80 (dd, *J* = 9.4, 4.2 Hz, 1H), 2.09 – 1.53 (m, 8H), 1.26 (dd, *J* = 6.2, 2.5 Hz, 6H).
 LCMS, [M+H]⁺ = 436.0.

Intermediate 2. Isopropyl (1S,3S)-3-((2-(5-(aminomethyl)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylate.



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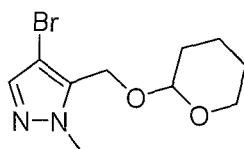
Intermediate 2A. (4-Bromo-1-methyl-1H-pyrazol-5-yl)methanol



A mixture of 4-bromo-1-methyl-1H-pyrazole-5-carboxylic acid (5.0 g, 24.4 mmol) and $\text{BH}_3 \cdot \text{THF}$ (36.6 mL of a 1 M solution in THF, 36.6 mmol) in THF (50 mL) was stirred at 50 °C for 2 days; at this point LCMS showed the completion of the reaction. The reaction was cooled to RT and cautiously quenched with aq. 1N HCl and stirred at RT for 1 h, after which the mixture was extracted with EtOAc (3 X 50 mL). The combined organic extracts were concentrated *in vacuo*. The residue was chromatographed (80 g SiO_2 ; continuous gradient from 0% to 100% EtOAc in hexanes, 25 min) to give the title compound (3.60 g, 18.9 mmol, 77 % yield) as a white solid. LCMS, $[\text{M}+\text{H}]^+ = 193.0$.

15

Intermediate 2B. 4-bromo-1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazole

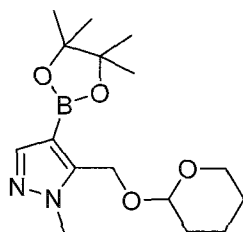


20

$p\text{-TsOH} \cdot \text{H}_2\text{O}$ (0.050 g, 0.262 mmol) was added to a RT solution of Intermediate 2A (1.0 g, 5.23 mmol) and 3,4-dihydro-2H-pyran (1.32 g, 15.7 mmol) in DCM (10 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred overnight at RT. The

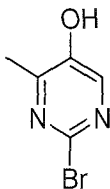
mixture was cooled to 0°C, neutralized with sat'd aq. NaHCO₃ to pH 7, then was partitioned between DCM (10 mL) and H₂O (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (40 g SiO₂; continuous
 5 gradient from 0%-80% EtOAc in hexanes over 14 min) to give the title compound (1.4 g, 5.09 mmol, 97 % yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.41 (s, 1H), 4.72 (d, *J* = 12.9 Hz, 1H), 4.65 (dd, *J* = 4.1, 3.0 Hz, 1H), 4.58 (d, *J* = 12.9 Hz, 1H), 3.93 (s, 3H), 3.88 (ddd, *J* = 11.6, 8.3, 3.1 Hz, 1H), 3.57 (dddd, *J* = 11.0, 5.0, 3.9, 1.4 Hz, 1H), 3.49 (d, *J* = 5.5 Hz, 2H), 1.85 – 1.75 (m, 1H), 1.75 – 1.66 (m, 1H), 1.66 – 1.48 (m, 4H).
 10 LCMS, [M+H]⁺ = 275.1.

Intermediate 2C. 1-Methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



15 Ar was vigorously bubbled through a stirred mixture of Intermediate 2B (550 mg, 2.00 mmol), KOAc (589 mg, 6.00 mmol) and B₂Pin₂ (761 mg, 3.00 mmol) in 1,4-dioxane (10 mL) for 5 min. Pd(dppf)Cl₂-CH₂Cl₂ (163 mg, 0.20 mmol) was added, and the reaction flushed with Ar, then was heated to 100 °C for 16 h; LCMS analysis after 16 h indicated that the reaction was complete. The reaction mixture was cooled to RT and
 20 partitioned between CH₂Cl₂ (20 mL) and H₂O (10 mL); the resulting mixture was stirred vigorously. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was used in the next step without further purification.

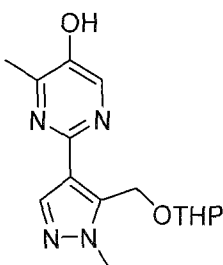
Intermediate 2D. 2-Bromo-4-methylpyrimidin-5-ol



25

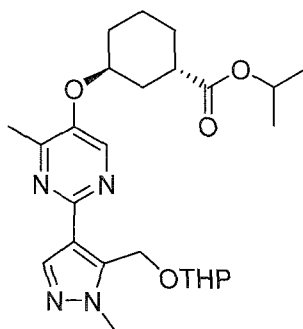
A mixture of 2-chloro-4-methylpyrimidin-5-ol (500 mg, 3.46 mmol) and HBr (30 wt.% in HOAc; 3 mL) was heated to 110 °C overnight, after which LCMS indicated the reaction was complete. The reaction mixture was cooled to RT, then was poured onto ice and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed
 5 with satd aq Na₂CO₃, water and brine, then was dried (Na₂SO₄) and concentrated in vacuo to afford the title compound (630 mg, 3.33 mmol, 96 % yield) as an off-white solid.
 LCMS, [M+H]⁺ = 189.1.

Intermediate 2E. 4-Methyl-2-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazol-4-yl)pyrimidin-5-ol
 10



A mixture of bis(di-tert-butyl(4-dimethylaminophenyl)phosphine) dichloropalladium (II) (101 mg, 0.14 mmol), Intermediate 2C (552 mg, 1.71 mmol), Intermediate 2D (270 mg, 1.43 mmol), aq. 2 M Na₂CO₃ (3.6 mL, 7.14 mmol) in MeCN (7
 15 mL) was heated at 100 °C in a microwave reactor for 1 h, then was cooled to RT, diluted with satd aq. NaHCO₃, and extracted with EtOAc (3 x 50 mL). The ombined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was chromatographed (80 g SiO₂, continuous gradient from 0%-90% EtOAc in hexanes) to provide the title compound (250 mg, 0.82 mmol, 58 % yield) as a beige solid.
 20 ¹H NMR (500 MHz, CDCl₃) δ 8.85 (d, J=1.42 Hz, 1H), 8.14 (d, J=1.41 Hz, 1H), 5.15 (m, 2H), 4.98 (m, 1H), 4.69 (m, 1H), 4.13 (s, 3H), 3.82 (ddd, J = 11.33, 7.90, 3.08 Hz, 1H), 3.49 (m, 1H), 2.74 (tt, J = 11.5, 3.67 Hz, 1H), 2.15 (m, 1H), 1.98 – 1.50 (m, 13H), 1.20 (m, 6H). [M+H]⁺ = 305.1. ¹H NMR (500 MHz, DMSO-d₆) δ 8.17 (s, 1H), 7.86 (s, 1H), 5.26 (d, J=11.9 Hz, 1H), 5.09 (d, J=11.9 Hz, 1H), 4.77 - 4.69 (m, 1H), 3.87 (s, 3H), 3.85 -
 25 3.77 (m, 2H), 2.37 (s, 3H), 1.73 - 1.39 (m, 6H).

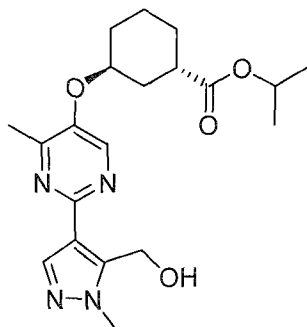
Intermediate 2F. Isopropyl (1S,3S)-3-((4-methyl-2-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)oxy)cyclohexane-1-carboxylate



A mixture of (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (435 mg, 1.73 mmol), toluene (8 mL) and Bu₃P (0.43 mL, 1.73 mmol) was stirred at RT for 30 min, after which Intermediate 2E (210 mg, 0.69 mmol) and isopropyl (1S,3R)-3-hydroxycyclohexane-1-carboxylate (231 mg, 1.24 mmol) were successively added. The reaction mixture was heated at 85 °C for 9 h, after which LC/MS indicated the formation of the desired product. The reaction was cooled to RT and diluted with CH₂Cl₂; the mixture was filtered and the filtrate was concentrated in *vacuo*. The crude oily product was chromatographed (80 g SiO₂; continuous gradient from 0% to 90% EtOAc/Hex over 25 min, hold at 90% for 20 min) to give the title compound (190 mg, 0.40 mmol, 58 % yield) as a light yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.98 (s, 1H), 8.09 (s, 1H), 5.51 (t, *J* = 6.90 Hz, 1H), 5.43 (s, 1H), 4.98 (m, 1H), 4.80 (d, *J* = 6.88, 2H), 4.07 (s, 3H), 2.72 (tt, *J* = 11.5, 3.67 Hz, 1H), 2.15 (m, 1H), 1.98 – 1.50 (m, 7H), 1.20 (m, 6H). LCMS, [M+H]⁺ = 473.2.

15

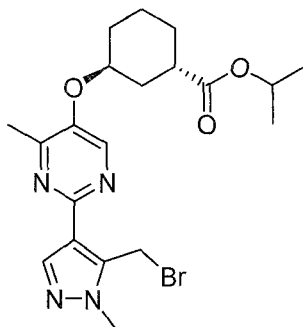
Intermediate 2G. Isopropyl (1S,3S)-3-((2-(5-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylate



A solution of Intermediate 2F (190 mg, 0.40 mmol) and PPTS (15 mg, 0.06 mmol) in MeOH (4 mL) was heated at 60 °C overnight, then was cooled to RT and concentrated in *vacuo*. Sat'd aq NaHCO₃ was added and the mixture was extracted with EtOAc (3 X 25 mL). The combined organic extracts were washed with H₂O and brine,

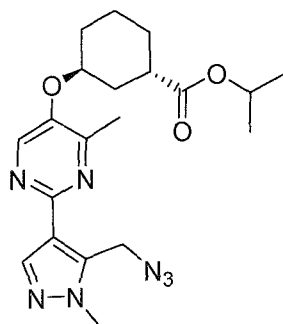
dried (MgSO_4) and concentrated *in vacuo*. The crude product was chromatographed (40 g SiO_2 , continuous gradient from 0%-100% EtOAc in hexanes) to provide the title compound (140 mg, 90 % yield) as a beige solid. LCMS, $[\text{M}+\text{H}]^+ = 389.2$.

- 5 Intermediate 2H. Isopropyl (1S,3S)-3-((2-(5-(bromomethyl)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylate



- 10 PBr_3 (0.09 mL, 0.90 mmol) was added to a solution of Intermediate 2G (140 mg, 0.36 mmol) in DME (4 mL) at 0 °C. The reaction was allowed to warm to RT and stirred at RT overnight, then was cooled to 0 °C and sat'd aq NaHCO_3 was cautiously added to quench the reaction and the pH was adjusted to ~7. The mixture was partitioned between EtOAc (200 mL) and H_2O (10 mL); the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo*. The crude product was chromatographed (40 g SiO_2 ; continuous gradient from 0% to 15 60% of EtOAc:hexanes over 20 min) to give the title compound (140 mg, 0.31 mmol, 86 % yield) as a colorless oil. LCMS, $[\text{M}+\text{H}]^+ = 453.0$.

Intermediate 2I. Isopropyl (1S,3S)-3-((2-(5-(azidomethyl)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylate



20

To a solution of Intermediate 2H (500 mg, 1.11 mmol) in DMF (2 mL) was added NaN_3 (72 mg, 1.11 mmol) and the reaction was stirred at 80 °C for 1 h; at this point

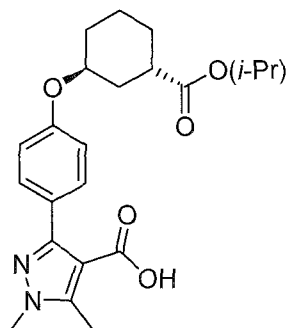
LCMS analysis indicated the reaction was complete. The reaction mixture was cooled to RT, partitioned between EtOAc and water (10 mL each), and the resulting mixture was stirred at RT for 15 min. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was chromatographed (24 g SiO₂; continuous gradient from 0% to 100% EtOAc in hexane over 12 min) to afford the title compound (368 mg, 0.890 mmol, 80 % yield) as a colorless oil. LCMS, [M + H]⁺ = 414.3. ¹H NMR (500 MHz, CDCl₃) δ 8.25 (s, 1H), 8.14 (s, 1H), 5.09 – 5.03 (m, 1H), 5.02 (s, 2H), 4.74 (dp, *J* = 5.2, 2.7 Hz, 1H), 3.96 (s, 3H), 2.78 (tq, *J* = 8.0, 4.1 Hz, 1H), 2.52 (s, 3H), 2.15 – 1.57 (m, 8H), 1.27 (dd, *J* = 6.3, 2.5 Hz, 6H).

10

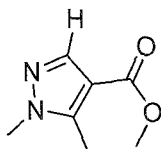
Intermediate 2

A solution of Intermediate 2I (128 mg; 0.31 mmol) and Ph₃P (81 mg, 0.31 mmol) in THF (2 mL) and H₂O (0.7 mL) was stirred at RT overnight; at this point LCMS analysis indicated the reaction was complete. EtOAc/water were added, and the mixture was stirred at RT for 15 min. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was chromatographed (12 g SiO₂; continuous gradient from 0% to 10% MeOH in CH₂Cl₂ for 20 min; flow rate = 30 mL/min) to give the title compound (97 mg, 0.25 mmol, 81 % yield) as a light brown oil. LCMS, [M+H]⁺ = 388.2.

20 Intermediate 3. 3-(4-(((1S,3S)-3-(isopropoxycarbonyl)cyclohexyl)oxy)phenyl)-1,5-dimethyl-1H-pyrazole-4-carboxylic acid



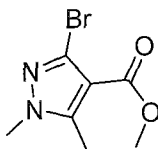
Intermediate 3A. Methyl 1,5-dimethyl-1H-pyrazole-4-carboxylate



25

To a 0°C solution of 1,5-dimethyl-1H-pyrazole-4-carboxylic acid (1.0 g, 7.14 mmol) in DCM/MeOH (7 mL each) was added 2M TMSCHN₂ in hexane (4.28 mL, 8.56 mmol). The reaction mixture was stirred at 0°C for 1 h, then was allowed to warm to RT and stirred at RT overnight, then was concentrated in vacuo. The crude product was
 5 chromatographed (80 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 20 min) to give the title compound (900 mg, 5.84 mmol, 82 % yield). LCMS, [M + H]⁺ = 155.2.

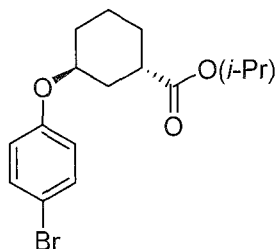
Intermediate 3B. Methyl 3-bromo-1,5-dimethyl-1H-pyrazole-4-carboxylate



10

To a solution of Intermediate 3A (1.10 g, 7.14 mmol) in MeCN (14.3 mL) was added HOAc (4.1 mL, 71.4 mmol) and Br₂ (0.44 mL, 8.56 mmol). The reaction mixture was stirred at RT for 16 h, then was washed with satd aq. sodium thiosulfate (20 mL) and extracted with EtOAc (3 X 20 mL). The combined organic extracts were dried (MgSO₄),
 15 concentrated in vacuo. The crude product was chromatographed (80 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 20 min) to give the title compound (400 mg, 25%). ¹H NMR (400 MHz, CDCl₃) δ 3.79 - 3.71 (m, 3H), 3.68 - 3.60 (m, 3H), 2.45 - 2.33 (m, 3H).

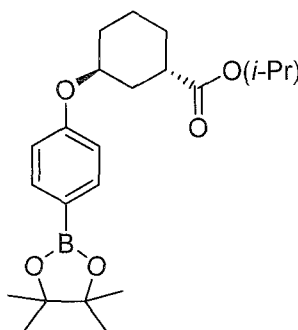
20 Intermediate 3C. Isopropyl (1S,3S)-3-(4-bromophenoxy)cyclohexane-1-carboxylate



To a solution of 4-bromophenol (500 mg, 2.89 mmol) and isopropyl (1S,3R)-3-hydroxycyclohexane-1-carboxylate (538 mg, 2.89 mmol) in toluene (5.8 mL) were successively added dropwise Bu₃P (2.20 mL, 8.67 mmol) and (E)-diazene-1,2-diylbis
 25 (piperidin-1-ylmethanone) (2.20 g, 8.67 mmol). The reaction mixture was heated at 50 °C for 2h, then was cooled to RT. Hexane (6 mL) was added to the mixture; a white

solid precipitated which was filtered off. The filtrate was concentrated in vacuo. The crude product was chromatographed (80 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexanes over 20 min) to give the title compound (400 mg, 1.17 mmol, 40.6 % yield). ¹H NMR (400 MHz, CDCl₃) δ 7.28 - 7.20 (m, 2H), 6.75 - 6.64 (m, 2H), 4.95 - 4.82 (m, 1H), 4.52 - 4.38 (m, 1H), 2.73 - 2.58 (m, 1H), 2.16 - 2.01 (m, 2H), 1.98 - 1.67 (m, 2H), 1.64 - 1.49 (m, 4H), 1.19 - 1.04 (m, 6H).

Intermediate 3D. Isopropyl (1S,3S)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)cyclohexane-1-carboxylate

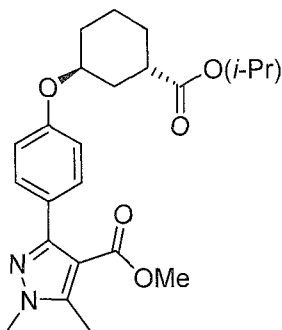


10

To a mixture of intermediate 3C (1.3 g, 3.8 mmol), bis-pinacolato diboron (1.5 g, 5.8 mmol), KOAc (1.15 g, 12 mmol) in 1,4-dioxane (8 mL) was added Xphos Pd G2 precatalyst (76 mg, 0.096 mmol) at RT. The mixture was heated at 80°C for 16 h, then was cooled to RT and washed with satd aq. NaHCO₃ (20 mL) and extracted with EtOAc (3 X 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude product was chromatographed (80 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 20 min) to give the title compound (1.00 g, 67%). ¹H NMR (400 MHz, CDCl₃) δ 7.81 - 7.71 (m, 2H), 7.00 - 6.88 (m, 2H), 5.09 - 4.96 (m, 1H), 4.74 - 4.62 (m, 1H), 2.89 - 2.73 (m, 1H), 2.11 - 2.04 (m, 1H), 1.97 - 1.86 (m, 2H), 1.80 - 1.70 (m, 1H), 1.67 - 1.59 (m, 2H), 1.40 - 1.34 (m, 12H), 1.32 - 1.28 (m, 2H), 1.27 - 1.21 (m, 6H).

20

Intermediate 3E. Methyl 3-(4-(((1S,3S)-3-(isopropoxycarbonyl)cyclohexyl)oxy)phenyl)-1,5-dimethyl-1H-pyrazole-4-carboxylate

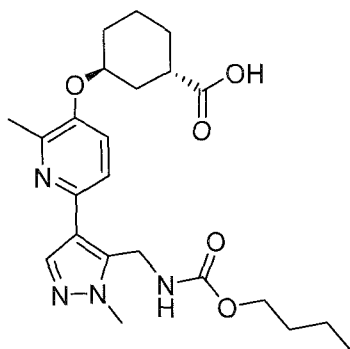


A mixture of Intermediate 3D (32 mg, 0.082 mmol), Intermediate 3B (19 mg, 0.082 mmol), and bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloro-palladium(II) (7 mg, 8 μ mol) in MeCN (1 mL) and water (0.05 mL) was stirred at 100°C
 5 in a microwave reactor for 1 h, then was cooled to RT. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2 x 50 mL); the combined organic layers were washed with water and brine (50 mL each), dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed (12 g SiO_2 ; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (20 mg, 0.048 mmol,
 10 59.2 % yield) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.61 - 7.46 (m, 2H), 7.08 - 6.85 (m, 2H), 5.14 - 4.94 (m, 1H), 4.73 - 4.58 (m, 1H), 3.90 - 3.82 (m, 3H), 3.81 - 3.70 (m, 3H), 2.88 - 2.74 (m, 1H), 2.62 - 2.48 (m, 3H), 2.17 - 2.03 (m, 1H), 1.97 - 1.87 (m, 3H), 1.84 - 1.72 (m, 1H), 1.65 - 1.53 (m, 3H), 1.33 - 1.20 (m, 6H).

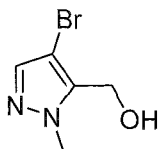
15 Intermediate 3

A mixture of Intermediate 3E (60 mg, 0.145 mmol) and LiI (97 mg, 0.724 mmol) in DMF (0.5 mL) was heated in a microwave reactor at 180°C for 30 min, then was cooled to RT and concentrated in vacuo. The residue was purified via preparative HPLC
 20 (C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 0% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H_2O :MeCN:TFA and B = 90:10:0.1 MeCN: H_2O :TFA) to give the title compound (20 mg, 0.050 mmol, 34.5 % yield). LCMS, $[\text{M} + \text{H}]^+ = 401.2$.

Example 1. (1S,3S)-3-(((6-(5-(((Butoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylic acid

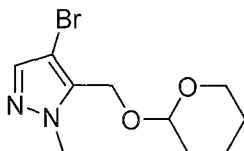


1A. (4-Bromo-1-methyl-1H-pyrazol-5-yl)methanol



5 A mixture of 4-bromo-1-methyl-1H-pyrazole-5-carboxylic acid (5.0 g, 24.4 mmol) and $\text{BH}_3 \cdot \text{THF}$ complex (36.6 mL, 36.6 mmol, 1.0 M in THF) in THF (50 mL) was stirred at 50 °C for 2 days, then was cooled to RT and cautiously quenched with 1N aq. HCl. The mixture was stirred at RT for 1 h, then was extracted with EtOAc (3X). The
 10 crude product was chromatographed (80 g SiO_2 ; 25 min continuous gradient from 0-100% EtOAc in hexanes) to afford the title compound (3.60 g, 18.9 mmol, 77 % yield) as a white solid. LCMS, $[\text{M} + \text{H}]^+ = 193.0$.

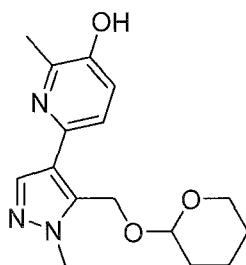
1B. 4-Bromo-1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazole



15 To a solution of 1A (3.60 g, 18.9 mmol) in CH_2Cl_2 (100 mL) was added 3,4-dihydro-2H-pyran (3.44 mL, 37.7 mmol) and PPTS (0.24 g, 0.94 mmol) and the reaction was stirred at RT overnight. Volatiles were removed in vacuo, and the crude product was chromatographed (120 g SiO_2 ; 25 min continuous gradient from 0-80% EtOAc in
 20 hexanes) to afford the title compound (4.80 g, 17.5 mmol, 93 % yield) as a clear oil. LCMS, $[\text{M} + \text{H}]^+ = 277.1$.

1C. 2-Methyl-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazol-4-

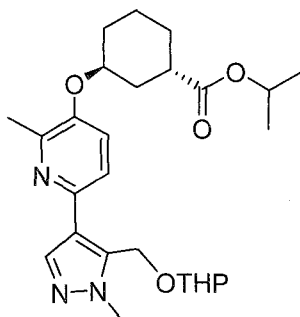
yl)pyridin-3-ol



To a degassed solution of 1B (1.0 g, 3.63 mmol), $B_2(OH)_4$ (0.65 g, 7.27 mmol) and KOAc (0.71 g, 7.27 mmol), ethylene glycol (0.61 mL, 10.9 mmol) in EtOH (18 mL) was added XPhos ligand (2 mg, 3.6 μ mol) and XPhos Pd 2nd generation catalyst (6 mg, 7.3 μ mol). The reaction vial was purged with Ar, sealed and stirred at 80 °C for 1 h, then was cooled to RT. K_3PO_4 (1.54 g, 7.27 mmol) was added and the reaction mixture was degassed with N_2 for 30 min, after which 6-bromo-2-methylpyridin-3-ol (1.03 g, 5.45 mmol) was added. The reaction was stirred at 80 °C for 16 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc and water; the aqueous phase was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (120 g SiO_2 ; continuous gradient over 20 min from 0-100% EtOAc in Hexanes) to afford the title compound (0.37 g, 1.20 mmol, 33 % yield) as a white solid. LCMS, $[M + H]^+ = 304.3$.

15

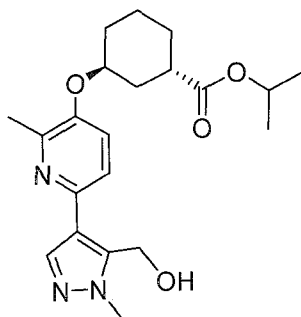
1D. (1S,3S)-Isopropyl 3-((2-methyl-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexanecarboxylate



To a pressure vial was added (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (0.50 g, 1.98 mmol), 1,4-dioxane (5 mL) and Bu_3P (0.49 mL, 1.98 mmol). The solution was stirred at RT for 30 min, after which (1S,3R)-isopropyl 3-hydroxycyclohexanecarboxylate (synthesized according to the procedure described in US2007/0197788A1; 0.22 g, 1.19 mmol) and 1C (0.20 g, 0.659 mmol) were added. The

reaction mixture was heated at 70-80 °C for 2 h, after which LC/MS indicated the formation of the desired product. The reaction was cooled to RT and partitioned between EtOAc/H₂O. The organic layer was filtered and concentrated *in vacuo*. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes over 15 min, hold at 50% for 10 min) to give the title compound (172 mg, 0.365 mmol, 55.3 % yield) as a clear oil. LCMS, [M + H]⁺ = 472.3.

1E. (1S,3S)-Isopropyl 3-(((6-(5-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylate

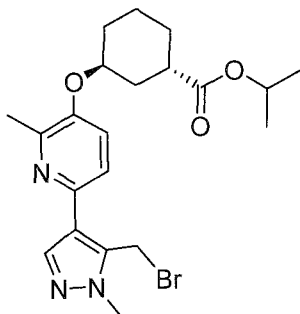


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To a solution of 1D (170 mg, 0.360 mmol) in MeOH (4 mL) was added PPTS (14 mg, 0.054 mmol). The reaction was heated at 60 °C overnight, then was cooled to RT. The reaction was concentrated *in vacuo* and partitioned between sat. aq. NaHCO₃ and EtOAc. The aqueous layer was extracted with EtOAc (2X0). The combined organic extracts were washed with water and brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was chromatographed (40 g SiO₂; 25 min. continuous gradient from 0-90% EtOAc in Hexanes) to afford the title compound (0.103 g, 74 % yield) as a colorless oil. LCMS, [M + H]⁺ = 388.2.

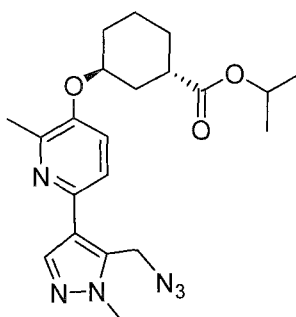
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20 1F. (1S,3S)-Isopropyl 3-(((6-(5-(bromomethyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylate



PBr₃ (0.06 mL, 0.665 mmol) was added to a solution of 1E (103 mg, 0.266 mmol) in DME (2.5 mL) at 0 °C. The reaction was stirred overnight at RT, then was cooled to 0 °C and neutralized with satd aq. NaHCO₃ to pH 7. The mixture was partitioned between EtOAc (50 mL) and water (10 mL), and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (12 g SiO₂; continuous gradient from 0% to 60% of EtOAc in hexanes for 15 min) to give the title compound (96 mg, 0.213 mmol, 80 % yield) as a white solid.

1G. (1S,3S)-Isopropyl 3-(((6-(5-(azidomethyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylate

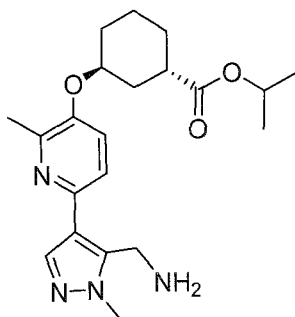


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To a solution of 1F (96 mg, 0.213 mmol) in DMF (1.8 mL) was added NaN₃ (35 mg, 0.533 mmol) and the reaction was stirred at 80 °C for 1 h, after which LCMS analysis indicated the reaction was complete. The reaction mixture was cooled to RT and partitioned between EtOAc and water, and the resulting mixture was stirred at RT for 15 min. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford the crude title compound, which was used in the next step without further purification. LCMS, [M + H]⁺ = 413.2.

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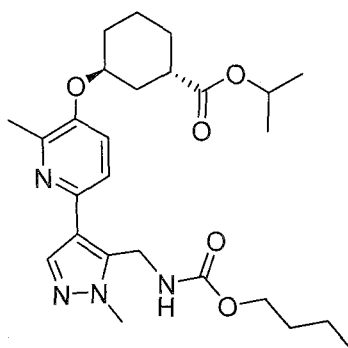
1H. (1S,3S)-Isopropyl 3-(((6-(5-(aminomethyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylate



To a solution of the crude 1G from the above reaction in THF (1.5 mL) and H₂O (0.50 mL) was added Ph₃P (62 mg, 0.234 mmol) and the reaction was stirred at RT overnight, after which LCMS analysis indicated that the reaction was complete. The reaction mixture was partitioned between EtOAc and water, and the resulting mixture was stirred at RT for 15 min. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was chromatographed (8 g SiO₂; 100% EtOAc for 10 min and then a continuous gradient from 0 % to 15 % MeOH in CH₂Cl₂ for 20 min; flow rate = 30 mL/min) to give the title compound (63 mg, 0.163 mmol, 77 % yield) as a beige oil.

LCMS, [M + H]⁺ = 387.2.

11. (1S,3S)-Isopropyl 3-(((6-(5-(((butoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylate



To a solution of 1H (12 mg, 0.031 mmol) in EtOAc (0.3 mL) and satd aq. NaHCO₃ (0.3 mL) was added butyl chloroformate (0.02 mL, 0.155 mmol) at RT. The mixture was stirred at RT overnight, then was concentrated in *vacuo* to give the crude title compound. LCMS [M + H]⁺ = 487.2.

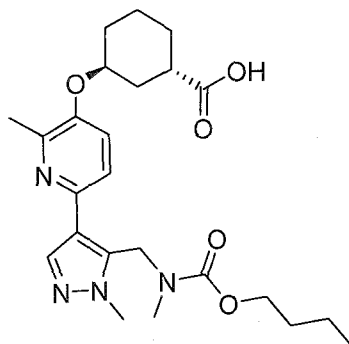
Example 1

To the above crude product 11 was added THF (0.8 mL)/H₂O (0.4 mL)/MeOH (0.4 mL) and LiOH.H₂O (7 mg, 0.155 mmol) at RT. The mixture was stirred at RT

overnight, then was concentrated in vacuo and diluted with H₂O (5 mL). The mixture was adjusted with 1N aq. HCl to pH ~5 and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 mL), dried (MgSO₄) and concentrated *in vacuo* to afford the crude title compound which was purified via preparative LC/MS: Column: Waters XBridge C18, 19 x 200 mm, 5- μ m particles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5- μ m particles; Mobile Phase A: 5:95 MeCN:H₂O with 0.1% TFA; Mobile Phase B: 95:5 MeCN:H₂O with 0.1% TFA; Gradient: 50-90% B over 20 min, then a 5-min hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound (7.4 mg, 0.016 mmol, 52 % yield). LCMS [M + H]⁺ = 445.3. ¹H NMR (500 MHz, DMSO-d₆) δ 7.73 (br. s., 1H), 7.64 (d, *J*=7.6 Hz, 2H), 7.35 - 7.23 (m, 5H), 7.05 (d, *J*=7.9 Hz, 2H), 5.01 (s, 2H), 4.74 - 4.66 (m, 1H), 4.14 (d, *J*=4.6 Hz, 2H), 2.67 - 2.54 (m, 1H), 2.20 (br. s., 3H), 1.96 - 1.40 (m, 8H). HPLC-4: RT = 1.33 min; HPLC-5: RT = 1.69 min; purity = 99%. hLPA1 IC₅₀ = 28 nM.

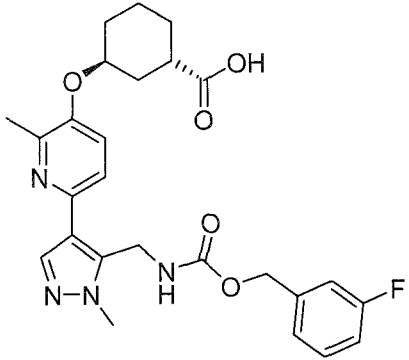
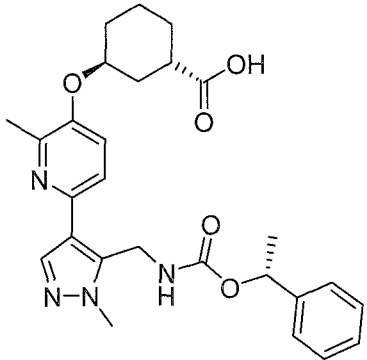
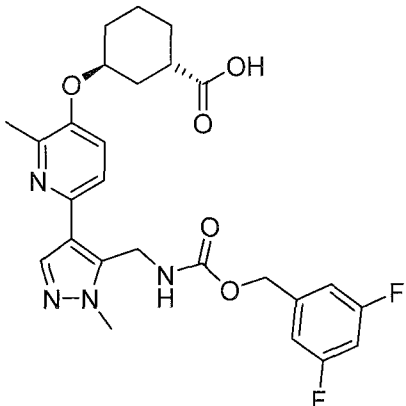
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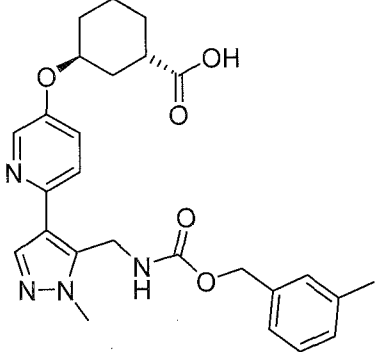
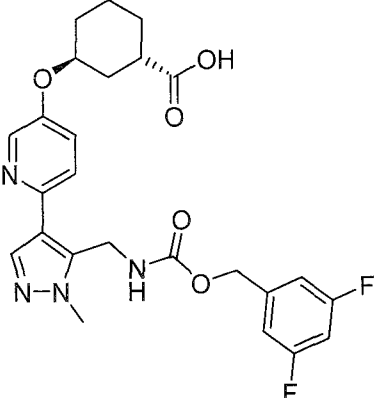
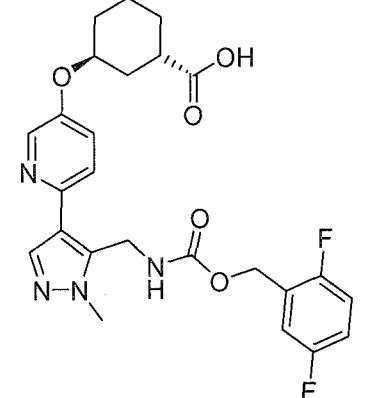
Example 2. (1S,3S)-3-(((6-(5-(((Butoxycarbonyl)(methyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylic acid

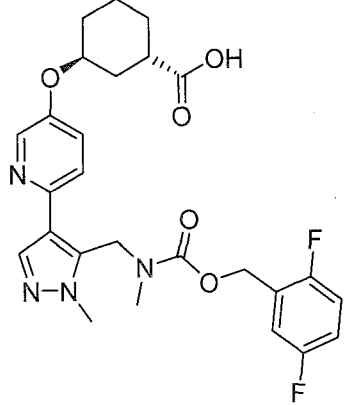
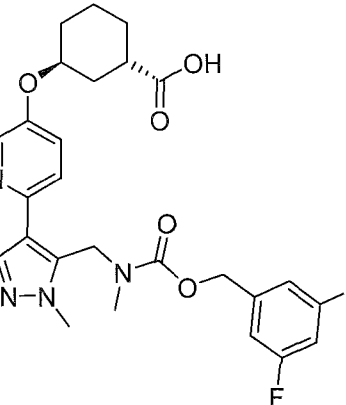
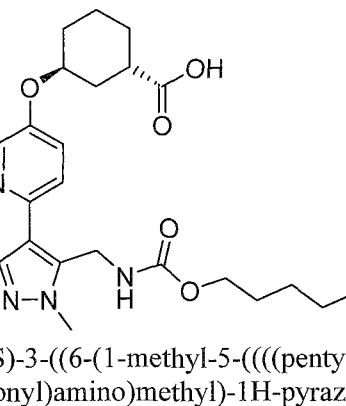


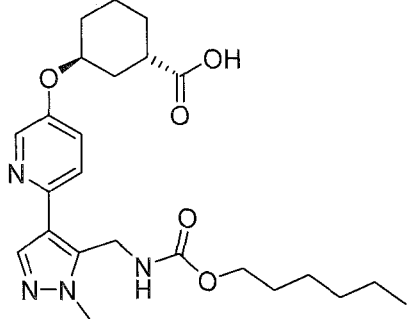
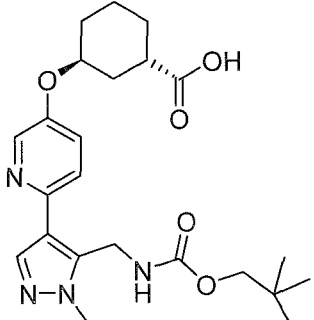
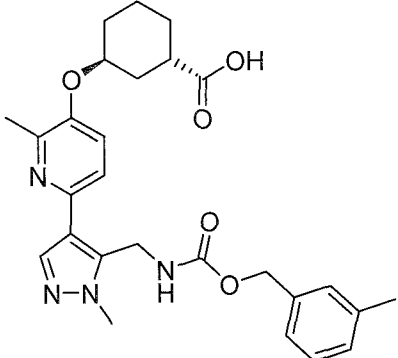
To a 0 °C solution of Example 1 (4.4 mg, 9.90 μ mol) in DMF (0.2 mL) under N₂ was added NaH (3 mg of a 60% dispersion in oil, 0.03 mmol) and the reaction mixture was stirred at RT for 30 min, then was cooled to 0 °C. MeI (2 μ L, 0.03 mmol) was added and the reaction was stirred at RT for 1 hour, after which LCMS showed that starting material had disappeared completely. Volatiles were removed in vacuo and the residue was dissolved in THF (0.8 mL)/H₂O (0.4 mL)/MeOH (0.4 mL). LiOH.H₂O (2 mg, 50 μ mol) was and the reaction mixture was stirred at RT overnight, then was concentrated in vacuo. The residue was diluted with H₂O (5 mL) and the aqueous mixture was adjusted with 1N aq. HCl to pH ~5 and extracted with EtOAc (3 x 5 mL).

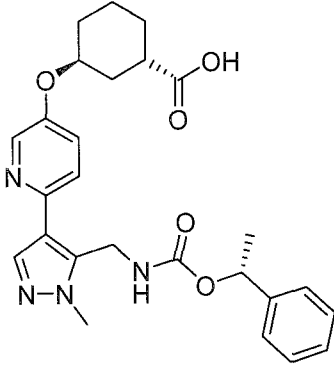
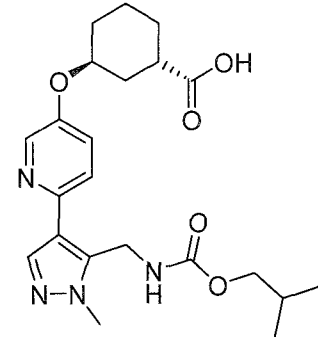
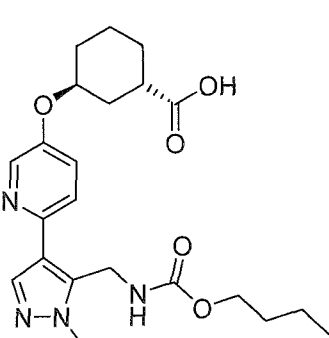
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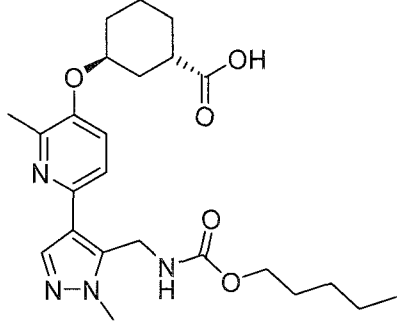
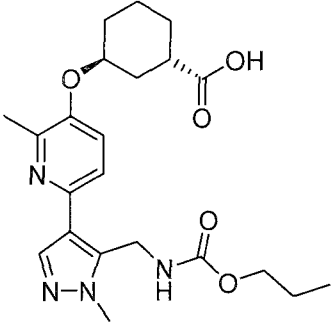
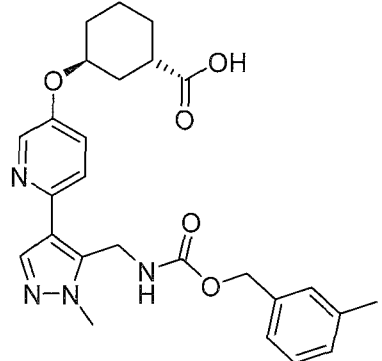
4	 <p>(1S,3S)-3-((6-(5-(((3-fluorobenzyl)oxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methyl-pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 497.2; ¹H NMR (400 MHz, CD₃OD): δ 7.76 (s, 1H), 7.35-7.41 (m, 2H), 7.02-7.16 (m, 3H), 5.10 (s, 2H), 4.74-7.49 (m, 1H), 4.66 (s, 2H), 3.96 (s, 3H), 2.78-2.83 (m, 1H), 2.50 (s, 3H), 2.09-2.13 (m, 1H), 1.89-1.96 (m, 3H), 1.61-1.78 (m, 4H); hLPA₁ IC₅₀ = 12 nM.</p>	Example 1
5	 <p>(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((R)-1-phenylethoxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 493.1; ¹H NMR (400 MHz, CD₃OD): δ 7.73 (s, 1H), 7.23-7.40 (m, 7H), 4.57-4.60 (m, 3H), 3.88 (s, 3H), 2.87-2.91 (m, 2H), 2.77-2.78 (m, 1H), 2.50 (s, 3H), 1.97-2.09 (m, 1H), 1.81-1.97 (m, 3H), 1.62-1.78 (m, 4H), 1.27 (d, J = 5.60 Hz, 3H); hLPA₁ IC₅₀ = 11 nM.</p>	Example 1
6	 <p>(1S,3S)-3-((6-(5-(((3,5-difluorobenzyl)oxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methyl-pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 515.1; ¹H NMR (400 MHz, CD₃OD): δ 7.74 (d, J = 6.00 Hz, 1H), 7.37-7.41 (m, 2H), 5.07 (s, 2H), 4.77-7.48 (m, 1H), 4.62 (s, 2H), 3.91 (s, 3H), 2.78-2.79 (m, 2H), 2.77-2.78 (m, 1H), 2.49 (s, 3H), 1.97-2.09 (m, 1H), 1.81-1.97 (m, 3H), 1.62-1.78 (m, 4H); hLPA₁ IC₅₀ = 7 nM.</p>	Example 1

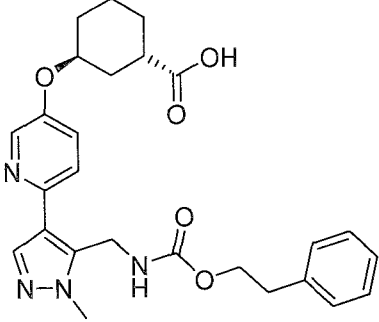
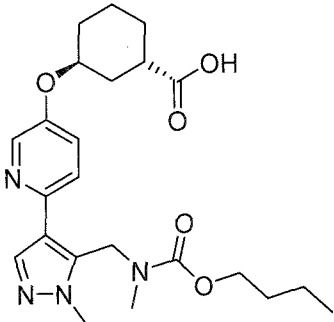
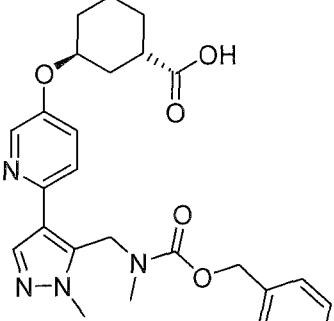
7	 <p>(1S,3S)-3-((6-(1-methyl-5-(((3-methylbenzyl)oxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 493.3; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.25 (br. S., 1 H), 7.75 (s, 1 H), 7.48 (br. S., 1 H), 7.40 (br. S., 1 H), 7.10 – 7.27 (m, 4 H), 5.10 (s, 2 H), 5.05 (br. S., 2 H), 4.72 (br. S., 1 H), 3.80 (br. S., 3 H), 2.74 – 2.85 (m, 1 H), 2.70 (s, 3 H), 2.34 (s, 3 H), 2.01 – 2.12 (m, 1 H), 1.82 – 1.98 (m, 3 H), 1.55 – 1.80 (m, 4 H); hLPA₁ IC₅₀ = 280 nM.</p>	<p>Example 1; via Intermediate 1</p>
8	 <p>(1S,3S)-3-((6-(5-(((3,5-difluorobenzyl)oxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 501.3; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.30 (d, J=3.01 Hz, 1 H), 7.78 (s, 1 H), 7.56 (d, J=8.53 Hz, 1 H), 7.43 (dd, J=8.78, 2.76 Hz, 1 H), 6.82 - 6.96 (m, 3 H), 5.07 (s, 2 H), 4.74 (br. s., 1 H), 4.65 (s, 2 H), 3.95 (s, 3 H), 2.73 - 2.86 (m, 1 H), 2.02 - 2.10 (m, 1 H), 1.83 - 2.00 (m, 3 H), 1.55 - 1.83 (m, 4 H); hLPA₁ IC₅₀ = 111 nM.</p>	<p>Example 1; via Intermediate 1</p>
9	 <p>(1S,3S)-3-((6-(5-(((2,5-difluorobenzyl)oxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 501.3; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.30 (d, J = 2.80 Hz, 1H), 7.77 (s, 1 H), 7.56 (d, J=9.04 Hz, 1 H), 7.42 (d, J=6.53 Hz, 1 H), 7.02 - 7.19 (m, 3 H), 5.12 (s, 2 H), 4.70-7.80 (m, 1 H), 4.65 (s, 2 H), 3.96 (s, 3 H), 2.78 - 2.84 (m, 1 H), 2.03 - 2.12 (m, 1 H), 1.84 - 2.01 (m, 3 H), 1.55 - 1.83 (m, 4 H); hLPA₁ IC₅₀ = 71 nM.</p>	<p>Example 1; via Intermediate 1</p>

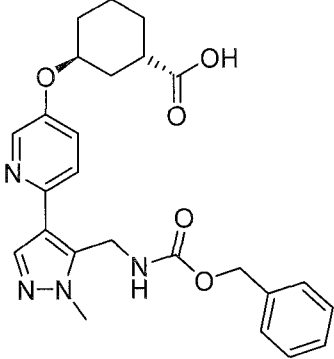
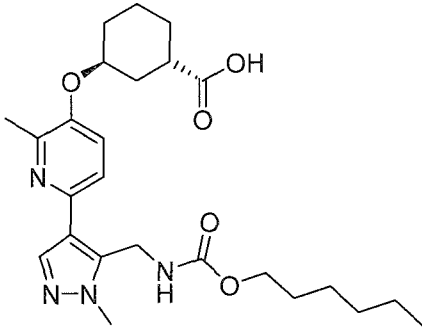
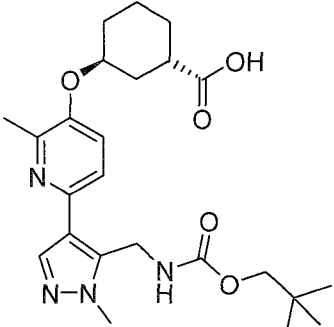
10	 <p>(1S,3S)-3-((6-(5-(((2,5-difluorobenzyl)oxy)carbonyl)(methyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 515.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.26 (d, J = 2.00 Hz, 1H), 7.78 (br. s., 1H), 7.51 (br. s., 1H), 7.41 (dd, J = 2.80, 8.80 Hz, 1H), 7.06 - 7.20 (m, 3H), 5.19 (s, 2H), 5.07 (br. s., 2H), 4.74 (br. s., 1H), 3.83 (br. s., 3H), 2.74 - 2.85 (m, 1H), 2.72 (s, 3H), 2.01 - 2.12 (m, 1H), 1.83 - 1.98 (m, 3H), 1.57 - 1.82 (m, 4H); hLPA₁ IC₅₀ = 1664 nM.</p>	Example 2; via Intermediate 1
11	 <p>(1S,3S)-3-((6-(5-(((3,5-difluorobenzyl)oxy)carbonyl)(methyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 515.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.26 (br. s., 1H), 7.76 (s, 1H), 7.50 (br. s., 1H), 7.41 (dd, J = 2.80, 8.60 Hz, 1H), 7.03-7.20 (m, 3H), 5.18 (s, 2H), 5.07 (s, 2H), 4.73 (br. s., 1H), 3.83 (s, 3H), 2.78 - 2.87 (m, 1H), 2.77 (s, 3H), 2.01 - 2.11 (m, 1H), 1.83 - 2.00 (m, 3H), 1.57 - 1.82 (m, 4H); hLPA₁ IC₅₀ = 703 nM.</p>	Example 2; via Intermediate 1
12	 <p>(1S,3S)-3-((6-(1-methyl-5-(((pentyl)oxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 445.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.33 (d, J=2.93 Hz, 1H), 7.79 (s, 1H), 7.59 (d, J=8.80 Hz, 1H), 7.46 (dd, J=8.68, 3.06 Hz, 1H), 4.71 - 4.79 (m, 1H), 4.62 (s, 2H), 4.04 (t, J=6.72 Hz, 2H), 3.98 (s, 3H), 2.75 - 2.89 (m, 1H), 2.02 - 2.14 (m, 1H), 1.84 - 2.02 (m, 3H), 1.51 - 1.84 (m, 6H), 1.33 (br. S., 4H), 0.86 - 0.95 (m, 3H); hLPA₁ IC₅₀ = 16 nM.</p>	Example 1; via Intermediate 1

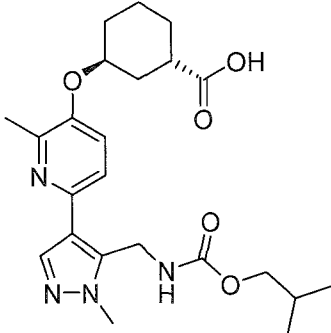
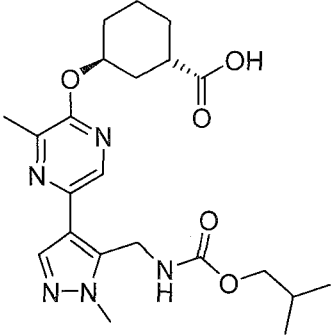
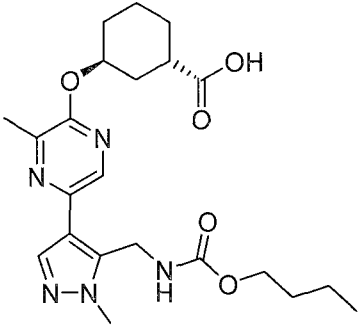
13	 <p>(1S,3S)-3-((6-(5-(((hexyloxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid</p>	<p>LCMS, $[M + H]^+ = 459.1$; 1H NMR (400 MHz, DMSO-d_6): δ 8.29 (d, $J=2.80$ Hz, 1H), 7.81 (s, 1H), 7.59 (d, $J=8.80$ Hz, 1H), 7.43 (dd, $J=8.40$ & 2.80 Hz, 1H), 7.30 - 7.40 (m, 1H), 4.72 (br. s., 1H), 4.59 (d, $J=5.20$ Hz, 2H), 3.94 (s, 2H), 3.89 (s, 3H), 2.60 - 2.70 (m, 1H), 1.70 - 2.00 (m, 4H), 1.45 - 1.70 (m, 6H), 1.15 - 1.30 (m, 6H), 0.83 (t, $J=7.2$ Hz, 3H); hLPA₁ IC₅₀ = 834 nM.</p>	<p>Example 1; via Intermediate 1</p>
14	 <p>(1S,3S)-3-((6-(1-methyl-5-(((neopentyloxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid</p>	<p>LCMS, $[M + H]^+ = 445.1$ 1H NMR (400 MHz, CD₃OD) δ ppm 8.33 (d, $J=2.45$ Hz, 1 H), 7.79 (s, 1 H), 7.59 (d, $J=8.80$ Hz, 1 H), 7.46 (dd, $J=8.80$, 2.93 Hz, 1 H), 4.71 - 4.79 (m, 1 H), 4.64 (s, 2 H), 3.98 (s, 3 H), 3.76 (s, 2 H), 2.77 - 2.88 (m, 1 H), 2.03 - 2.14 (m, 1 H), 1.86 - 2.03 (m, 3 H), 1.57 - 1.86 (m, 4 H), 0.92 (s, 9 H). hLPA₁ IC₅₀ = 207 nM.</p>	<p>Example 1; via Intermediate 1</p>
15	 <p>(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-methylbenzyl)oxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 493.1$; 1H NMR (400 MHz, CD₃OD): δ 7.83 (d, $J = 8.40$ Hz, 1H), 7.61-7.64 (m, 1H), 7.48 (d, $J = 9.60$ Hz, 1H), 4.76-4.78 (m, 3H), 4.05-4.08 (m, 5H), 3.45-3.53 (m, 2H), 3.2 (s, 3H), 2.59-2.62 (m, 1H), 2.44 (s, 3H), 1.99-2.05 (m, 1H), 1.75-1.90 (m, 3H), 1.48-1.63 (m, 4H); hLPA₁ IC₅₀ = 2 nM.</p>	<p>Example 1</p>

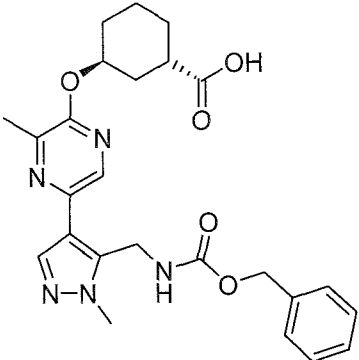
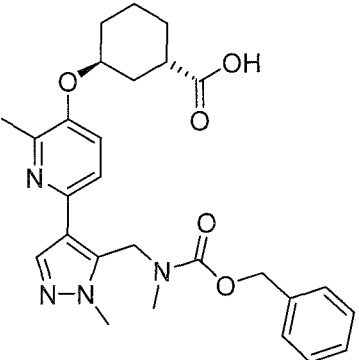
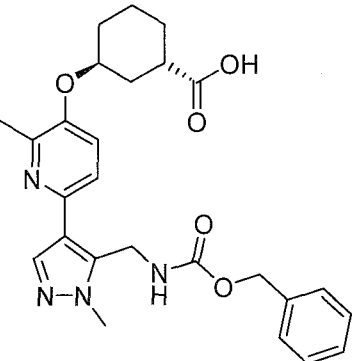
16	 <p>(1S,3S)-3-(((6-(1-methyl-5-((((R)-1-phenylethoxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 479.3$; $^1\text{H NMR}$ (400 MHz, CD_3OD) δ ppm 8.32 (d, $J=2.93$ Hz, 1 H), 7.78 (s, 1 H), 7.56 (d, $J=8.80$ Hz, 1 H), 7.43 (dd, $J=8.44, 2.81$ Hz, 1 H), 7.23 - 7.36 (m, 5 H), 5.73 (q, $J=6.40$ Hz, 1H), 4.76 (br. s., 1 H), 4.62 (br. s., 2 H), 3.91 (s, 3 H), 2.78 - 2.87 (m, 1 H), 2.03 - 2.13 (m, 1 H), 1.87 - 2.02 (m, 3 H), 1.57 - 1.85 (m, 4 H), 1.49 (d, $J=6.11$ Hz, 3 H); hLPA₁ IC₅₀ = 23 nM.</p>	Example 1; via Intermediate 1
17	 <p>(1S,3S)-3-(((6-(5-(((isobutoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 431.3$; $^1\text{H NMR}$ (400 MHz, CD_3OD) δ ppm 8.33 (d, $J=2.93$ Hz, 1 H), 7.79 (s, 1 H), 7.59 (d, $J=8.56$ Hz, 1 H), 7.46 (dd, $J=8.68, 3.06$ Hz, 1 H), 4.77 (br. s., 1 H), 4.63 (br. s., 2 H), 3.98 (s, 3 H), 3.83 (d, $J=6.60$ Hz, 2 H), 2.75 - 2.89 (m, 1 H), 2.02 - 2.14 (m, 1 H), 1.83 - 2.01 (m, 4 H), 1.56 - 1.83 (m, 4 H), 0.91 (d, $J=6.60$ Hz, 6 H); hLPA₁ IC₅₀ = 1637 nM.</p>	Example 1; via Intermediate 1
18	 <p>(1S,3S)-3-(((6-(5-(((butoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 431.3$; $^1\text{H NMR}$ (400 MHz, CD_3OD) δ ppm 8.33 (d, $J=2.45$ Hz, 1 H), 7.79 (s, 1 H), 7.58 (d, $J=8.80$ Hz, 1 H), 7.46 (dd, $J=8.68, 2.81$ Hz, 1 H), 4.77 (br. s., 1 H), 4.62 (s, 2 H), 4.04 (t, $J=6.60$ Hz, 2 H), 3.98 (s, 3 H), 2.76 - 2.88 (m, 1 H), 2.02 - 2.14 (m, 1 H), 1.86 - 2.02 (m, 3 H), 1.51 - 1.85 (m, 6 H), 1.29 - 1.44 (m, 2 H), 0.94 (t, $J=7.46$ Hz, 3 H); hLPA₁ IC₅₀ = 325 nM.</p>	Example 1; via Intermediate 1

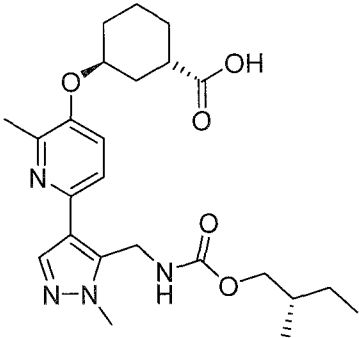
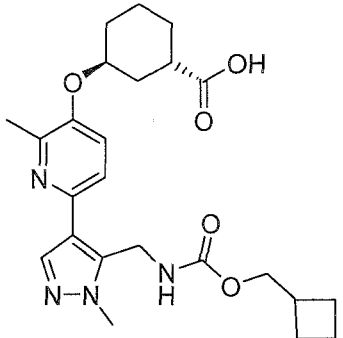
19	 <p>(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((pentyloxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 459.1; ¹H NMR (400 MHz, CD₃OD): δ 7.77 (s, 1H), 7.39-7.45 (m, 2H), 4.77-4.77 (m, 1H), 4.61 (s, 2H), 4.05 (t, J = 6.40 Hz, 2H), 3.97 (s, 3H), 2.79-2.84 (m, 1H), 2.52 (s, 3H), 2.09-2.17 (m, 1H), 1.89-1.97 (m, 3H), 1.55-1.78 (m, 6H), 1.31-1.34 (m, 4H), 0.92 (t, J = 6.80 Hz, 3H); hLPA₁ IC₅₀ = 4 nM.</p>	Example 1
20	 <p>(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((propoxycarbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 431.1; ¹H NMR (400 MHz, CD₃OD): δ 7.76 (s, 1H), 7.39 (q, J = 8.40 Hz, 2H), 4.75-4.77 (m, 1H), 4.60 (s, 2H), 4.01 (t, J = 6.40 Hz, 2H), 3.97 (s, 3H), 2.52 (s, 3H), 2.08-2.12 (m, 1H), 1.81-1.96 (m, 3H), 1.61-1.78 (m, 6H), 0.97 (t, J = 7.20 Hz, 2H); hLPA₁ IC₅₀ = 275 nM.</p>	Example 1
21	 <p>(1S,3S)-3-((6-(1-methyl-5-(((3-methylbenzyl)oxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 477.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.29 (d, J=3.01 Hz, 1 H), 7.77 (s, 1 H), 7.56 (d, J=8.03 Hz, 1 H), 7.42 (d, J=6.53 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.04 - 7.16 (m, 3 H), 5.03 (s, 2 H), 4.70-4.80 (m, 1 H), 4.63 (s, 2 H), 3.95 (s, 3 H), 2.74 - 2.86 (m, 1 H), 2.31 (s, 3 H), 2.01 - 2.11 (m, 1 H), 1.84 - 2.01 (m, 3 H), 1.56 - 1.83 (m, 4 H). hLPA₁ IC₅₀ = 182 nM.</p>	Example 1; via Intermediate 1

22	 <p>(1S,3S)-3-((6-(1-methyl-5-((phenethoxycarbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 479.2$; 1H NMR (400 MHz, CD_3OD) δ ppm 8.29 (d, $J=3.01$ Hz, 1 H), 7.77 (s, 1 H), 7.57 (d, $J=9.04$ Hz, 1 H), 7.44 (dd, $J=8.53, 3.01$ Hz, 1 H), 7.12 – 7.29 (m, 5 H), 4.70-4.80 (m, 1 H), 4.58 (s, 3 H), 4.23 (t, $J=7.03$ Hz, 2 H), 3.93 (s, 3 H), 2.87 (t, $J=6.78$ Hz, 2 H), 2.75 – 2.84 (m, 1 H), 2.00 2.10 (m, 1 H), 1.83 – 2.00 (m, 3 H), 1.55 – 1.83 (m, 4 H); hLPA₁ IC₅₀ = 355 nM.</p>	Example 1; via Intermediate 1
23	 <p>(1S,3S)-3-((6-(5-(((butoxycarbonyl)(methyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 445.1$; 1H NMR (400 MHz, $DMSO-d_6$): δ 12.18 (br. s., 1H), 8.27 (d, $J=2.80$ Hz, 1H), 7.86 (s, 1H), 7.59 (d, $J=8.40$ Hz, 1H), 7.43 (dd, $J=8.40$ & 2.80 Hz, 1H), 5.03 (s, 2H), 4.72 (br. s., 1H), 4.03 (t, $J=6.40$ Hz, 2H), 3.78 (s, 3H), 2.60 - 2.70 (m, 1H), 2.63 (s, 3H), 1.70 - 2.00 (m, 4H), 1.45 - 1.70 (m, 6H), 1.30 - 1.40 (m, 2H), 0.88 (t, $J=7.20$ Hz, 3H); hLPA₁ IC₅₀ = 243 nM.</p>	Example 2; via Intermediate 1
24	 <p>(1S,3S)-3-((6-(5-(((benzyloxy)carbonyl)(methyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 479.2$; 1H NMR (400 MHz, CD_3OD) δ ppm 8.26 (br. s., 1 H), 7.75 (s, 1 H), 7.49 (br. s., 1 H), 7.39 (d, $J=9.54$ Hz, 1 H), 7.30 - 7.38 (m, 5 H), 5.14 (s, 2 H), 5.06 (s, 2 H), 4.70 - 4.78 (m, 1 H), 3.80 (br. s., 3 H), 2.74 - 2.86 (m, 1 H), 2.70 (s, 3 H), 1.82 - 2.10 (m, 4 H), 1.56 - 1.82 (m, 4 H); hLPA₁ IC₅₀ = 204 nM.</p>	Example 2; via Intermediate 1

25	 <p>(1S,3S)-3-(((6-(5-(((benzyloxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 465.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.29 (d, J = 2.40 Hz, H), 7.77 (s, 1 H), 7.55 (d, J = 8.53 Hz, 1 H), 7.38 – 7.45 (m, 1 H), 7.31 (br. s, 5 H), 5.07 (s, 2 H), 4.72 – 4.78 (m, 1 H), 4.63 (s, 2 H), 3.95 (s, 3 H), 2.71 – 2.89 (m, 1 H), 2.01 – 2.13 (m, 1 H), 1.84 – 2.00 (m, 3 H), 1.56 – 1.83 (m, 4 H); hLPA₁ IC₅₀ = 20 nM.</p>	<p>Example 1; via Intermediate 1</p>
26	 <p>(1S,3S)-3-(((6-(5-(((hexyloxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 473.2; ¹H NMR (400 MHz, CD₃OD): δ 7.75 (s, 1H), 7.40 (q, J = 8.80 Hz, 2H), 4.74-4.77 (m, 1H), 4.60 (s, 2H), 4.03 (t, J = 10.00 Hz, 2H), 3.95 (s, 3H), 2.74-2.82 (m, 1H), 2.50 (s, 3H), 2.08-2.14 (m, 1H), 1.86-1.90 (m, 4H), 1.63-1.79 (m, 6H), 1.3-1.33 (m, 6H), 0.89 (t, J = 8.00 Hz, 3H); hLPA₁ IC₅₀ = 14 nM.</p>	<p>Example 1</p>
27	 <p>(1S,3S)-3-(((2-methyl-6-(1-methyl-5-(((neopentyloxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 459.1; ¹H NMR (400 MHz, CD₃OD): δ 7.75 (s, 1H), 7.40 (q, J = 8.80 Hz, 2H), 4.75-4.77 (m, 1H), 4.60 (s, 2H), 3.95 (s, 3H), 3.74 (s, 2H), 2.74-2.81 (m, 1H), 2.5 (s, 3H), 2.08-2.14 (m, 1H), 1.86-1.90 (m, 3H), 1.62-1.77 (m, 4H), 0.90 (s, 9H); hLPA₁ IC₅₀ = 22 nM.</p>	<p>Example 1</p>

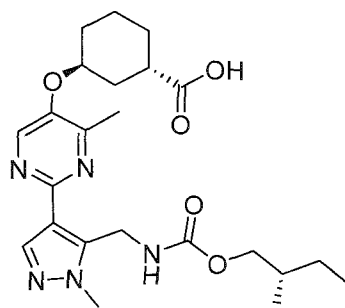
28	 <p>(1S,3S)-3-((6-(5-(((isobutoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 445.2; ¹H NMR (400 MHz, CD₃OD): δ 7.75 (s, 1H), 7.40 (q, J = 8.80 Hz, 2H), 4.75-4.77 (m, 1H), 4.60 (s, 2H), 3.95 (s, 3H), 3.82 (d, J = 6.40 Hz, 2H), 2.74-2.81 (m, 1H), 2.5 (s, 3H), 2.08-2.14 (m, 1H), 1.86-1.90 (m, 4H), 1.63-1.77 (m, 4H), 0.90 (d, J = 6.40 Hz, 6H); hLPA₁ IC₅₀ = 29 nM.</p>	Example 1
29	 <p>(1S,3S)-3-((5-(5-(((isobutoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 446.4; ¹H NMR (400 MHz, CD₃OD) d ppm 8.21 (d, J = 0.40 Hz, 1H), 7.81 (s, 1 H), 5.45 (br. s., 1 H), 4.65 (s, 2 H), 3.96 (s, 3 H), 3.81 (d, J=6.53 Hz, 2 H), 2.66 - 2.87 (m, 1 H), 2.51 (s, 3 H), 2.13 - 2.31 (m, 1 H), 1.91 - 2.06 (m, 2 H), 1.48 - 1.90 (m, 6 H), 0.90 (d, J=6.53 Hz, 6 H); hLPA₁ IC₅₀ = 1197 nM.</p>	Example 1
30	 <p>(1S,3S)-3-((5-(5-(((butoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 446.4; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.21 (d, J = 0.40 Hz, 1H), 7.81 (s, 1 H), 5.45 (br. s., 1 H), 4.46 (s, 2 H), 4.03 (t, J=6.53 Hz, 2 H), 3.96 (s, 3 H), 2.71 - 2.85 (m, 1 H), 2.51 (s, 3 H), 2.18 - 2.30 (m, 1 H), 1.93 - 2.07 (m, 2 H), 1.49 - 1.91 (m, 7 H), 1.25 - 1.44 (m, 2 H), 0.91 (t, J=7.53 Hz, 3 H); hLPA₁ IC₅₀ = 283 nM.</p>	Example 1

31	 <p>(1S,3S)-3-((5-(5-(((benzyloxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 480.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.22 (s, 1 H), 7.83 (s, 1 H), 7.20 - 7.40 (m, 5 H), 5.46 (br. s., 1 H), 5.09 (s, 2 H), 4.69 (s, 2 H), 3.96 (s, 3 H), 2.71 - 2.86 (m, 1 H), 2.50 (s, 3 H), 2.20 - 2.30 (m, 1 H), 1.91 - 2.06 (m, 2 H), 1.51 - 1.90 (m, 5 H); hLPA₁ IC₅₀ = 29 nM.</p>	Example 1
32	 <p>(1S,3S)-3-((6-(5-(((benzyloxy)carbonyl)(methyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methyl-pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 493.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 7.73 (br. s., 1 H), 7.23 - 7.54 (m, 7 H), 5.16 (s, 2 H), 5.09 (br. s., 2 H), 4.70-4.80 (m, 1 H), 3.82 (br. s., 3 H), 2.74 (s, 3 H), 2.63 - 2.81 (m, 1 H), 2.49 (s, 3 H), 2.02 - 2.10 (m, 1 H), 1.90-2.00 (m, 3 H), 1.56 - 1.81 (m, 4 H); hLPA₁ IC₅₀ = 211 nM.</p>	Example 2
33	 <p>(1S,3S)-3-((6-(5-(((benzyloxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 479.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 7.74 (s, 1 H), 7.25 - 7.44 (m, 7 H), 5.08 (s, 2 H), 4.75 - 4.79 (m, 1 H), 4.62 (s, 2 H), 3.94 (s, 3 H), 2.70 - 2.83 (m, 1 H), 2.48 (s, 3 H), 2.03 - 2.18 (m, 1 H), 1.83 - 2.00 (m, 3 H), 1.56 - 1.82 (m, 4 H); hLPA₁ IC₅₀ = 13 nM.</p>	Example 1

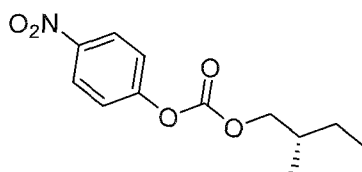
34	 <p>(1S,3S)-3-((2-methyl-6-(1-methyl-5-((((S)-2-methylbutoxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 459.0; ¹H NMR (500 MHz, DMSO-d₆) δ 7.79 (s, 1H), 7.61 - 7.51 (m, 2H), 4.82 - 4.73 (m, 1H), 4.59 - 4.48 (m, 2H), 3.90 - 3.70 (m, 5H), 2.66 - 2.57 (m, 1H), 2.45 (br. s., 3H), 1.90 - 1.00 (m, 11H), 0.86 - 0.76 (m, J=6.1 Hz, 6H); hLPA₁ IC₅₀ = 20 nM.</p>	Example 1
35	 <p>(1S,3S)-3-((6-(5-((((cyclobutyl-methoxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-2-methyl-pyridin-3-yl)oxy)cyclohexane-carboxylic acid</p>	<p>LCMS [M + H]⁺ = 456.9; ¹H NMR (500 MHz, DMSO-d₆) δ 7.78 (s, 1H), 7.47 - 7.33 (m, 2H), 4.76 - 4.68 (m, 1H), 4.59 (d, J=4.9 Hz, 2H), 3.97 - 3.89 (m, 2H), 3.85 (s, 3H), 2.65 - 2.56 (m, 1H), 2.40 (s, 3H), 2.01 - 1.41 (m, 15H); hLPA₁ IC₅₀ = 10 nM.</p>	Example 1

Example 36. (1S,3S)-3-((4-methyl-2-(1-methyl-5-((((S)-2-methylbutoxy)carbonyl)amino)methyl)-1H-pyrazol-4-yl)pyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid

5



36A. (S)-2-methylbutyl (4-nitrophenyl) carbonate



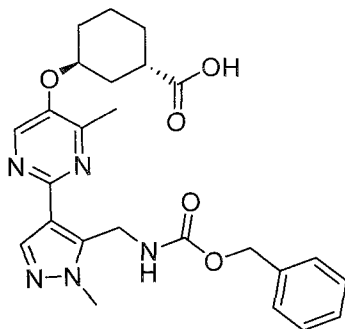
To a solution of (S)-2-methylbutan-1-ol (400 mg, 4.54 mmol) and 4-nitrophenyl chloro-formate (1.37 g, 6.8 mmol) in THF (8 mL) was added pyridine (1.1 mL, 13.6 mmol) at RT. A white solid was formed. The reaction mixture was stirred at RT for 24 h, then was concentrated *in vacuo*. The crude product was purified by chromatographed (24 g SiO₂, continuous gradient from 0 to 20% EtOAc in hexanes over 12 min) to afford the title compound (1.1g, 4.34 mmol, 96 % yield) as a slightly colored solid. LCMS, [M + Na]⁺ = 480.3. ¹H NMR (500 MHz, CDCl₃) δ 8.42 – 8.16 (m, 2H), 7.50 – 7.36 (m, 2H), 4.21 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.12 (dd, *J* = 10.4, 6.8 Hz, 1H), 1.82 – 1.82 (m, 1H), 1.58 – 1.49 (m, 1H), 1.34 – 1.24 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H).

Example 36

To a RT solution of Intermediate 2 (5 mg, 0.013 mmol) and (S)-2-methylbutyl (4-nitro-phenyl)carbonate (5 mg, 0.019 mmol) in THF (0.2 mL) was added iPr₂NEt (7 μL, 0.039 mmol). The reaction mixture was stirred for 4 h at RT, after which THF (0.5 mL)/H₂O (0.5 mL)/MeOH (0.5 mL) and LiOH·H₂O (3 mg, 0.071 mmol) were added. The reaction mixture was stirred at RT overnight, then was concentrated *in vacuo*. The residue was diluted with H₂O (2 mL), and the mixture was adjusted with 1N aq. HCl to pH ~5 and extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (2 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by preparative LC/MS: Column: XBridge Phenyl, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 MeCN:H₂O with 0.1% TFA; Mobile Phase B: 95:5 MeCN:H₂O with 0.1% TFA; Gradient: a 0-min hold at 30% B, 30-70% B over 19 min, then a 5-min hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound (TFA salt; C₂₃H₃₃N₅O₅·C₂HF₃O₂, 5.2 mg, 66 % yield). Its estimated purity by LCMS analysis was 95%. LCMS, [M + H]⁺ = 460.3. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 7.88 (s, 1H), 7.33 (br s, 1H), 4.83 (s, 1H), 4.75 (d, *J* = 5.5 Hz, 2H), 3.87 (s, 3H), 3.84 – 3.69 (m, 2H), 2.64 (td, *J* = 10.3, 5.0 Hz, 1H),

2.42 (s, 3H), 2.06 – 1.47 (m, 9H), 1.34 (s, 1H), 1.15 – 1.02 (m, 1H), 0.89 – 0.74 (m, 6H).
hLPA1 IC₅₀ = 31 nM.

Example 37. (1S,3S)-3-((2-(5-(((benzyloxy)carbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid

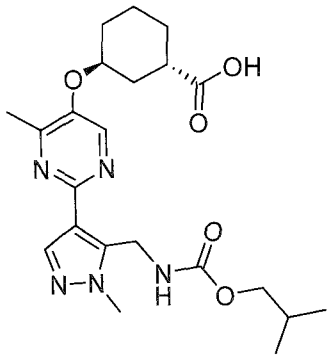


To a RT solution of Intermediate 2 (5 mg, 0.013 mmol) and benzyl chloroformate (3 μ L, 0.019 mmol) in THF (0.2 mL) was added iPr₂NEt (7 μ L, 0.039 mmol). The reaction mixture was stirred for 10 min at RT, after which THF (0.5 mL)/H₂O (0.5 mL)/MeOH (0.2 mL) and LiOH.H₂O (3 mg, 0.071 mmol) were added. The reaction mixture was stirred at RT overnight, then was concentrated *in vacuo*. The residue was diluted with H₂O (2 mL), and the mixture was adjusted with 1N aq. HCl to pH ~5 and extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (2 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by preparative LC/MS: Column: XBridge C18, 200 mm x 19 mm, 5- μ m particles; Mobile Phase A: 5:95 MeCN:H₂O with 0.1% TFA; Mobile Phase B: 95:5 MeCN:H₂O with 0.1% TFA; Gradient: a 0-min hold at 27% B, 27-67% B over 20 min, then a 4-min hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound (TFA salt; C₂₅H₂₉N₅O₅·C₂HF₃O₂, 4.8 mg, 60 % yield; 96% purity by LCMS). Its estimated purity by LCMS, [M + H]⁺ = 480.3. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.40 (s, 1H), 7.88 (s, 1H), 7.49 (s, 1H), 7.36 – 7.23 (m, 5H), 5.01 (s, 2H), 4.80 (s, 1H), 4.76 (d, *J* = 5.6 Hz, 2H), 3.87 (s, 3H), 2.67 – 2.59 (m, 1H), 2.40 (s, 3H), 2.04 – 1.43 (m, 8H). hLPA1 IC₅₀ = 16 nM.

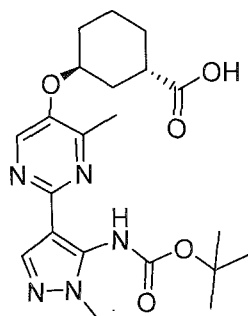
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Example 38 in Table 2 was synthesized according to the procedures described for the preparation of Example 37.

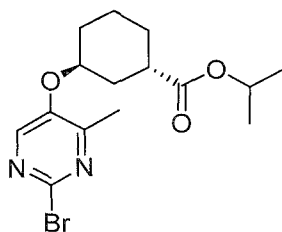
Table 2

Ex #	Structure & Name	Analytical & Biology Data
38	 <p>(1S,3S)-3-((2-(5-(((isobutoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS, $[M+H]^+ = 446.1$; 1H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.88 (s, 1H), 7.28 - 7.12 (m, 1H), 4.82 - 4.77 (m, 1H), 4.73 (br d, $J=5.5$ Hz, 2H), 3.88 (s, 3H), 3.73 (br d, $J=6.6$ Hz, 2H), 2.62 (br t, $J=9.6$ Hz, 1H), 2.42 (s, 3H), 2.03 - 1.46 (m, 9H), 0.82 (br d, $J=6.3$ Hz, 6H); hLPA$_1$ IC$_{50} = 218$ nM.</p>

Example 39. (1S,3S)-3-((2-(5-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid



39A. Isopropyl (1S,3S)-3-((2-bromo-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylate

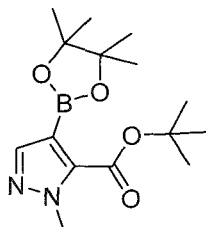


10

A mixture of (*E*)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (3.47 g, 13.8 mmol), toluene (30 mL) and Bu $_3$ P (3.44 mL, 13.8 mmol) was stirred at RT in a pressure vial for 30 min, after which 2-bromo-4-methylpyrimidin-5-ol (1.30 g, 6.88 mmol) and isopropyl (1S,3R)-3-hydroxycyclohexane-1-carboxylate (2.31 g, 12.38 mmol) were

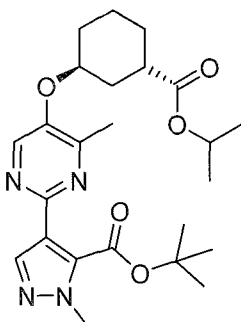
successively added. The reaction mixture was heated at 85 °C for 9 h, then was cooled to RT and diluted with DCM (10 mL). The mixture was filtered and the filtrate was concentrated in vacuo. The crude oily product was chromatographed (120 g SiO₂; continuous gradient from 0% to 90% EtOAc:hexane over 25 min, hold at 90% for 20 min) to provide the title compound (1.80 g, 5.04 mmol, 73.3 % yield) as a light yellow oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.32 (d, *J* = 3.7 Hz, 1H), 4.90 (p, *J* = 6.4 Hz, 1H), 4.80 (s, 1H), 2.70 – 2.59 (m, 1H), 2.38 (s, 3H), 2.01 – 1.46 (m, 8H), 1.18 (d, *J* = 6.3 Hz, 6H). [M+H]⁺ = 357.

10 39B. tert-butyl 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-5-carboxylate



Ar was vigorously bubbled through a stirred mixture of 39A (1.5 g, 5.74 mmol), KOAc (1.69 g, 17.2 mmol) and B₂pin₂ (2.19 g, 8.62 mmol) in 1,4-dioxane (20 mL) for 5 min. Pd(dppf)Cl₂-CH₂Cl₂ (0.47 g, 0.57 mmol) was added and the reaction flask was flushed with Ar. The reaction was heated at 100 °C for 16 h; at this point LCMS analysis indicated that the reaction was complete. The reaction mixture was cooled to RT; DCM and H₂O were added (20 mL each) and the resulting mixture was stirred vigorously. The organic layer was dried (Na₂SO₄), and concentrated in vacuo. The crude title compound was used in the next step without further purification. [M+H]⁺ = 309.2.

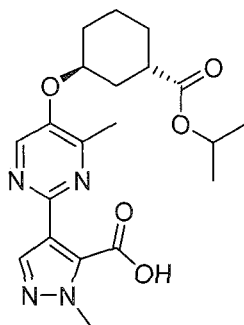
39C. Tert-butyl 4-(5-(((1S,3S)-3-(isopropoxycarbonyl)cyclohexyl)oxy)-4-methylpyrimidin-2-yl)-1-methyl-1H-pyrazole-5-carboxylate



A mixture of bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium (II) (0.169 g, 0.239 mmol), 39B (0.884 g, 2.87 mmol) and 39A (0.854 g, 2.39 mmol) in aq. 2 M Na₂CO₃ (6.0 mL, 12 mmol) and MeCN (12 mL) was heated at 100 °C in a microwave reactor for 1 h, then was cooled to RT. The mixture was diluted with satd aq. NaHCO₃ and extracted with EtOAc (3x10 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. The crude product was chromatographed (80 g SiO₂, continuous gradient from 0%-90% EtOAc:hexanes) to provide the title compound (1.08 g, 2.36 mmol, 98 % yield) as a beige solid. [M+H]⁺ = 459.3.

10

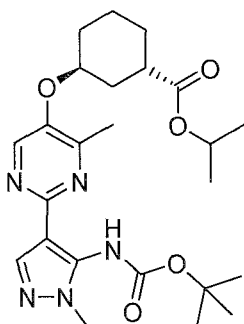
39D. 4-(5-(((1S,3S)-3-(isopropoxycarbonyl)cyclohexyl)oxy)-4-methylpyrimidin-2-yl)-1-methyl-1H-pyrazole-5-carboxylic acid



To a solution of 39C (1.08 g, 2.36 mmol) in DCM (20 mL) was added TFA (9.07 mL, 118 mmol) dropwise. The reaction was stirred at RT for 20 h, then was concentrated *in vacuo* to afford the crude title compound (1.20 g, 2.89 mmol, >100% yield) as a colored oil, which was used in the next step without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.62 (s, 1H), 8.14 (s, 1H), 4.94 – 4.87 (m, 2H), 4.12 (s, 3H), 2.72 – 2.62 (m, 1H), 2.49 (s, 3H), 2.08 – 1.44 (m, 8H), 1.19 (dd, *J* = 6.4, 1.9 Hz, 6H). [M+H]⁺ = 403.2.

20

39E. Isopropyl (1S,3S)-3-((2-(5-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylate



A mixture of crude 39D (600 mg, 1.49 mmol), $(\text{PhO})_2\text{PON}_3$ (0.58 mL, 2.68 mmol), 2-methylpropan-2-ol (331 mg, 2.23 mmol) and Et_3N (0.83 mL, 5.95 mmol) in toluene (3 mL) was stirred at 80 °C for 2 h, then was cooled to RT and concentrated in vacuo. The crude product was chromatographed (80 g SiO_2 ; continuous gradient from 0% to 100% EtOAc:hexane over 25 min) to afford the title compound (248 mg, 0.524 mmol, 35.2 % yield) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) (~1 : 1 mixture of rotamers) δ 8.71 (s, 1H), 8.23 (s, 0.5H), 8.04 (s, 0.5H), 5.05 (p, $J = 6.3$ Hz, 1H), 4.76 (s, 0.5H), 4.72 (s, 0.5H), 3.89 (s, 3H), 2.82 – 2.72 (m, 1H), 2.51 (br s, 3H), 2.15 – 1.47 (m, 8H), 1.27 (br s, 15H). $[\text{M}+\text{H}]^+ = 474.3$.

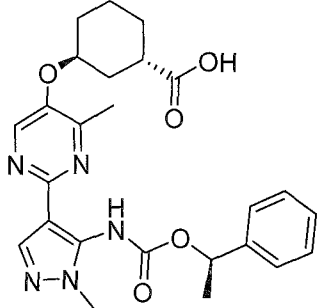
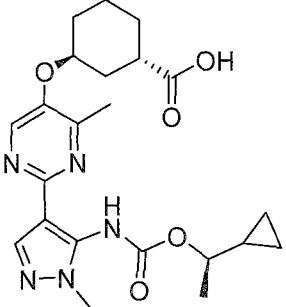
Example 39

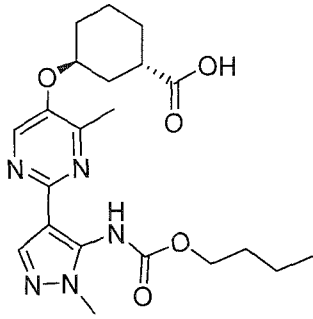
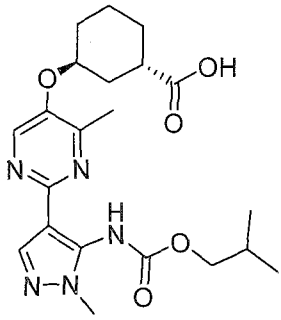
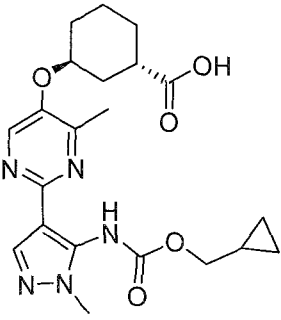
A mixture of 39E (10 mg, 0.021 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (9 mg, 0.22 mmol) in THF (0.5 mL), MeOH (0.5 mL), and water (0.5 mL) was stirred at RT for 72 h, then was concentrated in vacuo. The residue was taken up in EtOAc (2 mL)/ H_2O (1mL), and the solution was adjusted to pH ~ 5 with 1N aq. HCl. The mixture was extracted with EtOAc (3 x 2 mL); the combined organic extracts were dried (MgSO_4) and concentrated in vacuo. The residue was dissolved in DMF and purified via preparative LC/MS: Column: XBridge C18, 200 mm x 19 mm, 5- μm particles; Mobile Phase A: 5:95 MeCN: H_2O with 0.1% TFA; Mobile Phase B: 95:5 MeCN: H_2O with 0.1% TFA; Gradient: a 0-min hold at 18% B, 18-58% B over 20 min, then a 4-min hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound as a TFA salt ($\text{C}_{21}\text{H}_{29}\text{N}_5\text{O}_5\cdot\text{C}_2\text{HF}_3\text{O}_2$, 0.6 mg, 5% yield. Its estimated purity by LCMS analysis was 97%. LCMS, $[\text{M} + \text{H}]^+ = 432.3$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.43 (s, 1H), 7.87 (s, 1H), 4.80 (s, 1H), 3.66 (s, 3H), 2.39 (s, 3H), 1.93 – 1.48 (m, 8H), 1.40 (s, 9H). (The $-\text{CH}$

α to the carboxylic acid are not observed due to water-suppression). hLPA₁ IC₅₀ = 1518 nM.

The following examples in Table 3 was synthesized according to the procedures described for the preparation of Example 39.

Table 3

Ex #	Structure & Name	Analytical & Biological Data
40	 <p data-bbox="352 987 983 1088">(1S,3S)-3-((4-methyl-2-(1-methyl-5-(((R)-1-phenylethoxy)carbonyl)amino)-1H-pyrazol-4-yl)pyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p data-bbox="1015 757 1401 1025">LCMS, [M + H]⁺ = 480.3; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.27 (s, 1H), 7.90 (s, 1H), 7.54 – 7.11 (m, 5H), 5.73 (s, 1H), 4.78 (s, 1H), 3.67 (s, 3H), 2.66 – 2.56 (m, 1H), 2.32 (s, 3H), 2.02 – 1.32 (m, 11H); hLPA₁ IC₅₀ = 105 nM.</p>
41	 <p data-bbox="352 1449 975 1581">(1S,3S)-3-((2-(5-(((R)-1-cyclopropylethoxy)carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p data-bbox="1015 1200 1394 1536">LCMS [M + H]⁺ = 444.1; ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.12 (s, 1H), 7.65 (s, 1H), 4.55 (br s, 1H), 3.99 (q, <i>J</i> = 6.7 Hz, 1H), 3.44 (s, 3H), 2.45 – 2.35 (m, 1H), 2.16 (s, 3H), 1.78 – 1.23 (m, 8H), 0.99 (d, <i>J</i> = 5.8 Hz, 3H), 0.75 (s, 1H), 0.33 – 0.11 (m, 2H), 0.03 (br s, 2H); hLPA₁ IC₅₀ = 80 nM.</p>

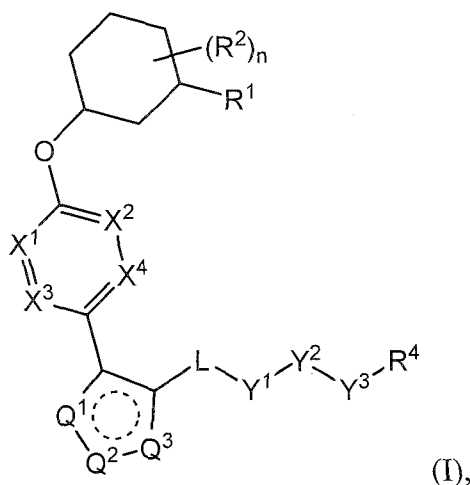
42	 <p>(1S,3S)-3-((2-(5-((butoxycarbonyl) amino)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 432.3$; $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.90 (s, 1H), 4.80 (s, 1H), 4.03 (br s, 2H), 3.69 (s, 3H), 2.70 – 2.61 (m, 1H), 2.40 (s, 3H), 2.04 – 1.43 (m, 10H), 1.27 (br s, 2H), 0.86 (t, $J = 8.2$ Hz, 3H); hLPA₁ IC₅₀ = 239 nM.</p>
43	 <p>(1S,3S)-3-((2-(5-((isobutoxy-carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 431.9$; $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.90 (s, 1H), 4.80 (s, 1H), 3.82 (br s, 2H), 3.66 (s, 3H), 2.64 – 2.57 (m, 1H), 2.36 (s, 3H), 2.01 – 1.34 (m, 9H), 0.79 (br s, 6H); hLPA₁ IC₅₀ = 564 nM.</p>
44	 <p>(1S,3S)-3-((2-(5-(((cyclopropyl-methoxy)carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-4-methylpyrimidin-5-yl)oxy)cyclohexane-1-carboxylic acid</p>	<p>LCMS $[M + H]^+ = 430.3$; $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.69 (s, 1H), 4.60 (s, 1H), 3.72 – 3.58 (m, 2H), 3.47 (s, 3H), 2.42 – 2.35 (m, 1H), 2.17 (s, 3H), 1.80 – 1.13 (m, 8H), 0.85 (s, 1H), 0.26 (br s, 2H), 0.01 (br s, 2H); hLPA₁ IC₅₀ = 995 nM.</p>

Other features of the invention should become apparent in the course of the above descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof. The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be

taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an
5 additional embodiment.

What is claimed is:

1. A compound according to Formula (I):



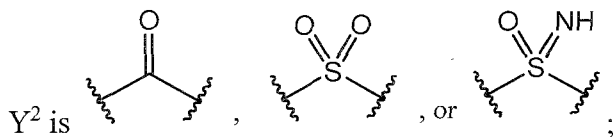
or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof,
wherein

X^1 , X^2 , X^3 , and X^4 are each independently CR^6 or N; provided that no more than two of X^1 , X^2 , X^3 , or X^4 are N;

Q^2 is N or NR^{5a} ;

one of Q^1 and Q^3 is CR^5 , and the other is N or NR^{5a} ; and the dashed circle denotes optional bonds forming an aromatic ring;

Y^1 is O or NR^3 ;



Y^3 is O or NR^{4a} ; provided that (1) Y^1 and Y^3 are not both O, and (2) when Y^2 is C(O), Y^1 is not O;

L is a covalent bond or C_{1-4} alkylene substituted with 0 to 4 R^7 ;

R^1 is $(-CH_2)_aR^9$;

a is an integer of 0 or 1;

R^2 is each independently halo, cyano, hydroxyl, amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkoxyalkyl, haloalkoxyalkyl, or haloalkoxy;

n is an integer of 0, 1, or 2;

R^3 and R^{4a} are independently hydrogen, C_{1-6} alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^4 is C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} deuterated alkyl, C_{1-10} alkenyl, C_{3-8} cycloalkyl, 6 to 10-membered aryl, 3 to 8-membered heterocyclyl, $-(C_{1-6}$ alkylene)-(C_{3-8} cycloalkyl), $-(C_{1-6}$ alkylene)-(6 to 10-membered aryl), $-(C_{1-6}$ alkylene)-(3 to 8-membered heterocyclyl), or $-(C_{1-6}$ alkylene)-(5 to 6-membered heteroaryl); wherein each of the alkyl, alkylene, alkenyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, by itself or as part of other moiety, is independently substituted with 0 to 3 R^8 ; or alternatively, R^3 and R^4 , taken together with the N and O atoms which they are attached, form a 4 to 9-membered heterocyclic ring moiety which is substituted with 0 to 3 R^8 ; or alternatively, (R^3 and R^{5a}) or (R^3 and R^5), taken together with the atoms to which they are attached to, form a 5 to 8-membered heterocyclic ring moiety which is substituted with 0 to 3 R^8 ;

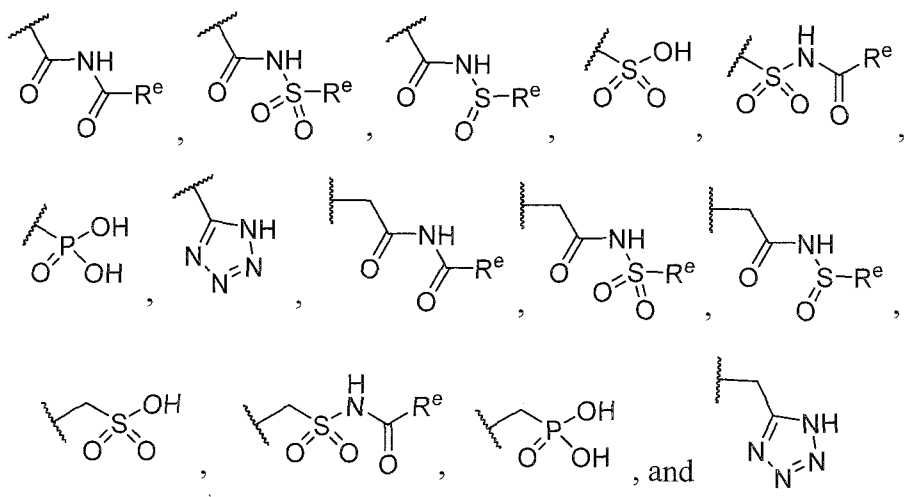
R^{5a} is hydrogen, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^5 and R^6 are each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^7 is halo, oxo, cyano, hydroxyl, amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^8 are each independently deuterium, halo, hydroxyl, amino, cyano, C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5 to 6-membered heteroaryl; or alternatively, two R^8 , taken together with the atom(s) to which they are attached, form a 3 to 6-membered carbocyclic ring or a 3 to 6-membered heterocyclic ring each of which is independently substituted with 0 to 3 R^{12} ;

R^9 is selected from $-\text{CN}$, $-\text{C}(\text{O})\text{OR}^{10}$, $-\text{C}(\text{O})\text{NR}^{11a}\text{R}^{11b}$,



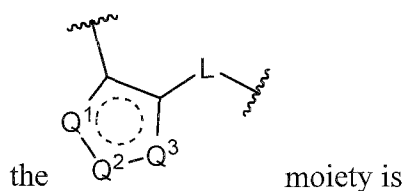
R^e is C_{1-6} alkyl, C_{3-6} cycloalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, or haloalkoxyalkyl;

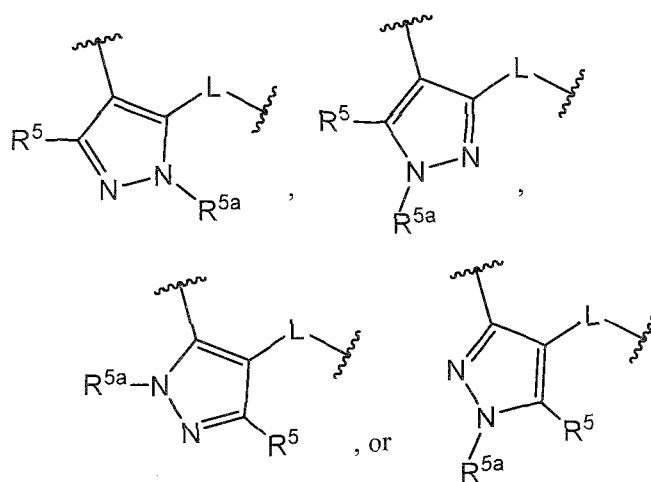
R^{10} is hydrogen or C_{1-10} alkyl; and

R^{11a} and R^{11b} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; and

R^{12} is halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, phenyl, or 5 to 6-membered heteroaryl.

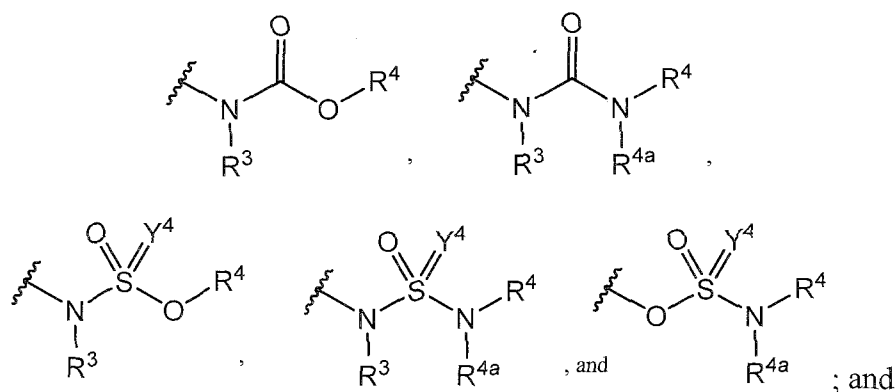
2. The compound according to claim 1, wherein





2A. The compound according to claim 1 or 2, wherein

the $\text{---Y}^1\text{---Y}^2\text{---Y}^3\text{---R}^4$ moiety is selected from



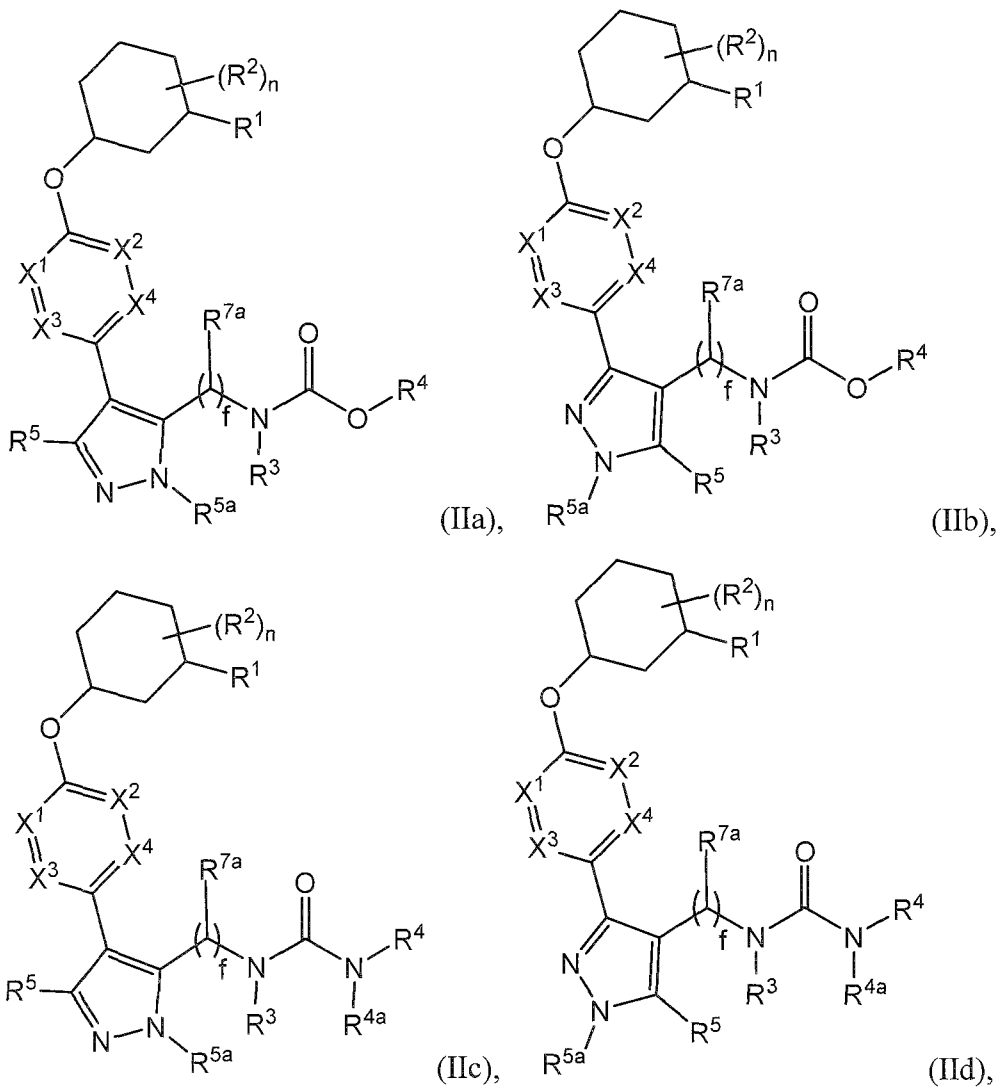
Y^4 is O or NH.

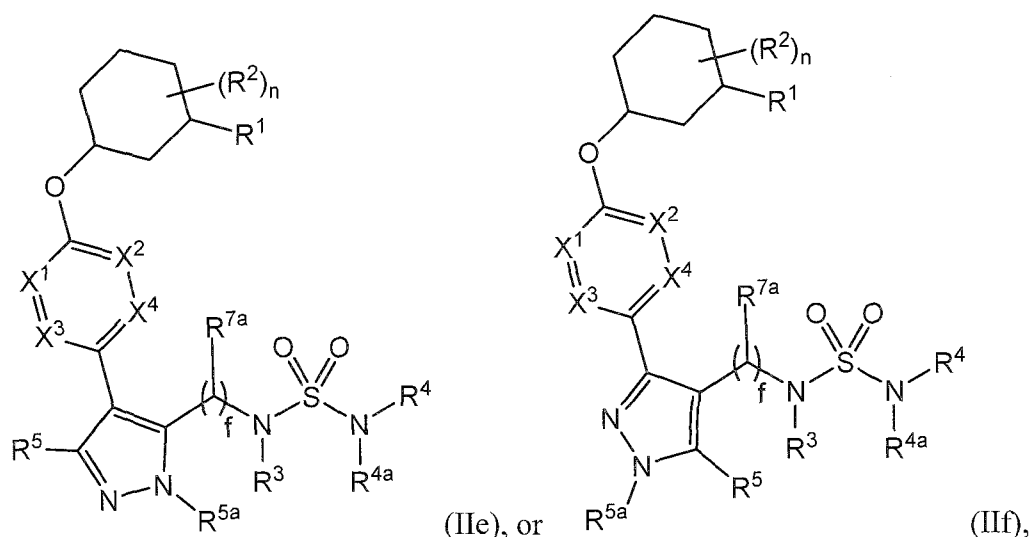
3. The compound according to claim 1 or 2, wherein n is 0.
4. The compound according to any one of claims 1 to 3, wherein R^1 is CO_2H .
5. The compound according to any one of claims 1 to 4, wherein R^5 is hydrogen.
6. The compound according to any one of claims 1 to 5, wherein R^{5a} is C_{1-4} alkyl.
7. The compound according to any one of claim 1 to 6, wherein

R^4 is C_{1-10} alkyl, C_{1-10} haloalkyl, C_{3-6} cycloalkyl, $-(C_{1-4}$ alkylene)-(C_{3-6} cycloalkyl), or benzyl; wherein the alkyl, alkylene, cycloalkyl, and benzyl are each independently substituted with 0 to 3 R^8 ; and

R^8 is each independently halo, hydroxyl, amino, cyano, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy, or phenyl.

8. The compound according to any one of claims 1 to 7, which is represented by Formula (IIa), (IIb), (IIc), (IId), (IIe), or (IIf):





each R^{7a} is independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} heterocyclyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

f is an integer of 1, 2, or 3;

n is 0 or 1;

R^3 and R^{4a} are each independently hydrogen or C_{1-4} alkyl;

R^5 and R^{5a} are each independently hydrogen or C_{1-4} alkyl; or alternatively, (R^3 and R^{5a}) or (R^3 and R^5), taken together with the atoms to which they are attached to, form a 6 to 8-membered heterocyclic ring moiety; and

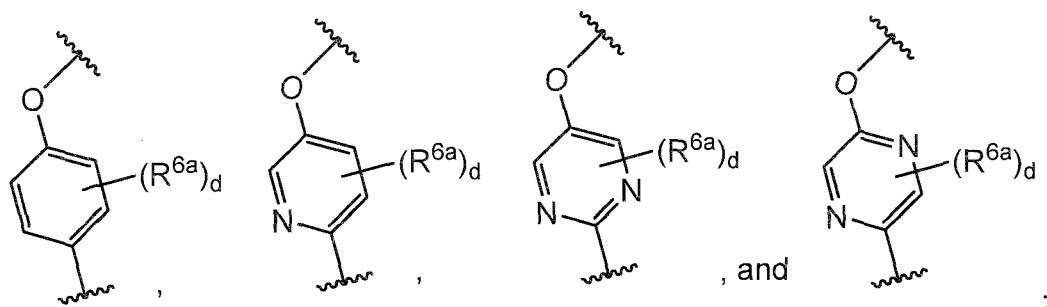
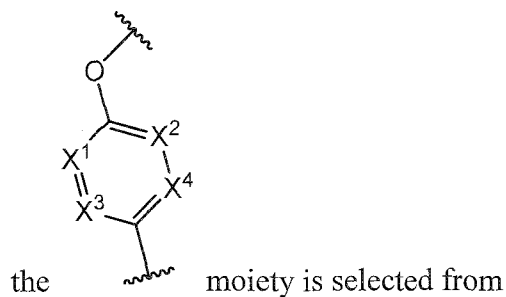
R^1 , R^2 , n , R^4 , X^1 , X^2 , X^3 , and X^4 are the same as defined in any one of claims 1 to 7.

9. The compound according to claim 8, wherein X^1 is CR^6 , where R^6 is hydrogen or C_{1-4} alkyl.

10. The compound according to claims 8 or 9, wherein X^3 is N.

11. The compound according to claims 8 or 9, wherein X^1 , X^2 , X^3 , and X^4 are CR^6 , where each R^6 is independently hydrogen or C_{1-4} alkyl.

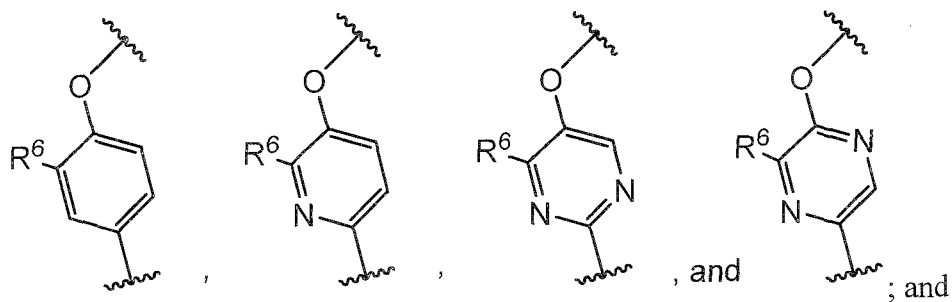
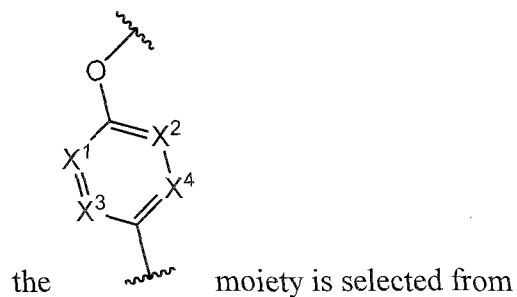
12. The compound according to any one of claims 8 to 11, wherein



R^{6a} is each independently halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy; and

d is an integer of 0, 1, or 2.

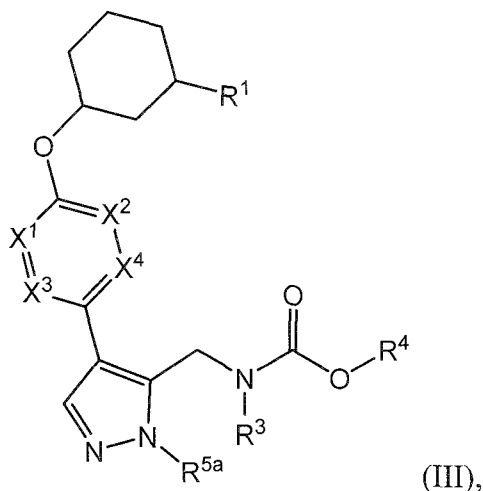
13. The compound according to claim 12, wherein



R^6 is each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy.

14. The compound according to any one of claims 8 to 13, wherein f is 1.

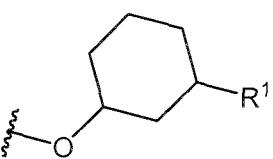
15. The compound according to any one of claims 1 to 14, which is represented by Formula (III):

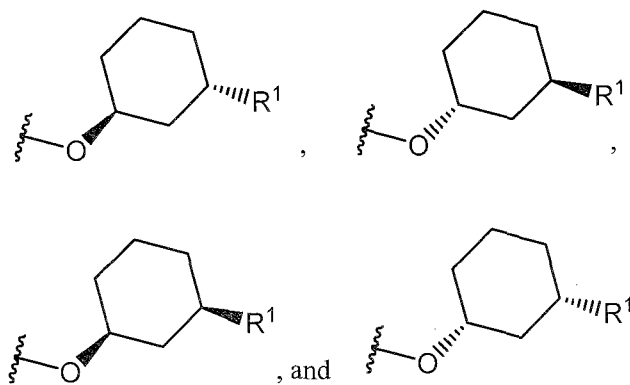


R^3 is methyl;

R^{5a} is methyl; or alternatively, R^3 and R^{5a} , taken together with the atoms to which they are attached to, form a 6 or 7-membered heterocyclic ring moiety; and

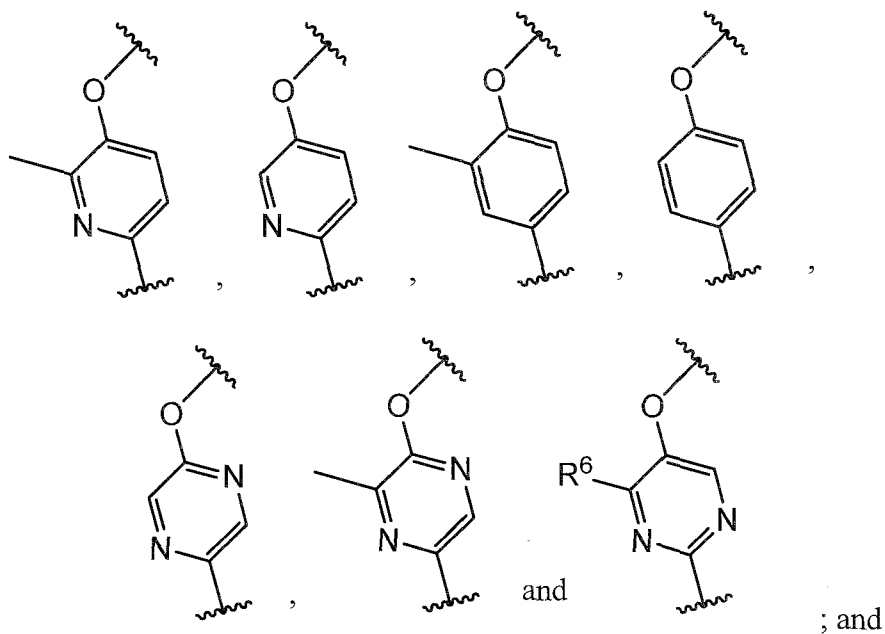
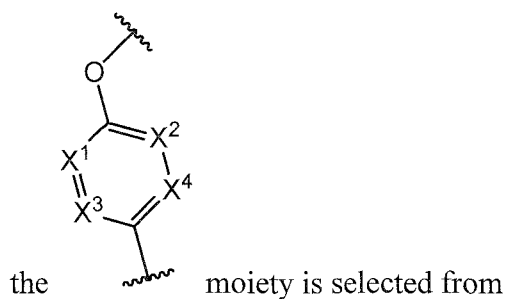
R^1 , R^4 , X^1 , X^2 , X^3 , and X^4 are the same as defined in any one of claims 1 to 15.

16. The compound according to claim 15, wherein the  moiety is selected from



17. The compound according to claim 15 or 16, wherein R^1 is CO_2H .

18. The compound according to any one of claims 15 to 17, wherein



R^6 is hydrogen, CH_3 , or CH_2CH_3 .

19. The compound according to any one of claims 15 to 18, wherein

R^4 is C_{3-10} alkyl, C_{3-10} haloalkyl, C_{3-6} cycloalkyl, $-(C_{1-4}$ alkylene)-(C_{1-3} alkoxy), $-(C_{1-4}$ alkylene)-(C_{3-6} cycloalkyl), or $-(C_{1-4}$ alkylene)-phenyl; wherein the alkyl, alkylene, cycloalkyl, and phenyl are each independently substituted with 0 to 3 R^8 ; and

R^8 is each independently halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy.

20. The compound according to any one of claims 15 to 19, wherein

R^4 is C_{3-10} alkyl, C_{3-10} haloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, $-(CHR^{8a})_{1-2}$ -cyclopropyl, $-(CHR^{8a})$ -cyclobutyl, or $-CH_2$ -phenyl; wherein the cyclopropyl and cyclobutyl are each substituted with 0 to 2 R^8 , and the phenyl is substituted with 0 to 2 halo selected from fluoro and chloro;

R^8 is each independently methyl, ethyl, propyl, or cyclopropyl; and

R^{8a} is each independently hydrogen or methyl.

21. The compound according to claim 1, which is selected from any one of the Examples as described in the specification, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof.

22. A pharmaceutical composition comprising one or more compounds according to any one of claims 1 to 21, or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable carrier or diluent.

23. A compound according to any one of claims 1 to 21, or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, for use in therapy.

24. A compound or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 21, or a pharmaceutical composition as claimed in claim 22 for use in treating a disease, disorder, or condition associated with dysregulation of lysophosphatidic acid receptor 1 (LPA₁).

25. The compound or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or composition for use according to claim 24, wherein the disease,

disorder, or condition is pathological fibrosis, transplant rejection, cancer, osteoporosis, or inflammatory disorders.

26. The compound or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or composition for use according to claim 25, wherein the pathological fibrosis is pulmonary, liver, renal, cardiac, dermal, ocular, or pancreatic fibrosis.

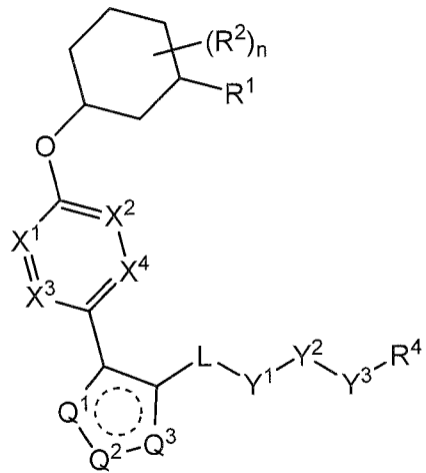
27. The compound or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or composition for use according to claim 24, wherein the disease, disorder, or condition is idiopathic pulmonary fibrosis (IPF), non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, diabetic kidney disease, and systemic sclerosis.

28. The compound or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or composition for use according to claim 25, wherein the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.

29. A compound according to any one according to claims 1 to 21, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition as claimed in claim 22 for use in treating fibrosis in a mammal in need thereof.

30. The compound or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or composition for use according to claim 29, wherein the fibrosis is idiopathic pulmonary fibrosis (IPF), nonalcoholic steatohepatitis (NASH), chronic kidney disease, diabetic kidney disease, and systemic sclerosis.

31. A compound according to any one according to claims 1 to 21, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition as claimed in claim 22 for use in treating lung fibrosis (idiopathic pulmonary fibrosis), asthma, chronic obstructive pulmonary disease (COPD), renal fibrosis, acute kidney injury, chronic kidney disease, liver fibrosis (non-alcoholic steatohepatitis), skin fibrosis, fibrosis of the gut, breast cancer, pancreatic cancer, ovarian cancer, prostate cancer, glioblastoma, bone cancer, colon cancer, bowel cancer, head and neck cancer, melanoma, multiple myeloma, chronic lymphocytic leukemia, cancer pain, tumor metastasis, transplant organ rejection, scleroderma, ocular fibrosis, age related macular degeneration (AMD), diabetic retinopathy, collagen vascular disease, atherosclerosis, Raynaud's phenomenon, or neuropathic pain in a mammal in need thereof.



(I)