



(51) International Patent Classification:

C07D 493/08 (2006.01) A61P 11/00 (2006.01)

A61K 31/4155 (2006.01) A61P 19/10 (2006.01)

A61K 31/42 (2006.01) A61P 35/00 (2006.01)

(21) International Application Number:

PCT/US2019/051272

(22) International Filing Date:

16 September 2019 (16.09.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/732,588 18 September 2018 (18.09.2018) US

(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY

[US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543 (US).

(72) Inventors: CHENG, Peter Tai Wah; c/o Bristol-Myers

Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US). SHI, Jun; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US). TAO, Shiwei; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US). ZHANG, Hao; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US).

(74) Agent: SUN, Jing G. et al.; Bristol-Myers Squibb Company,

Route 206 and Province Line Road, Princeton, New Jersey 08543 (US).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

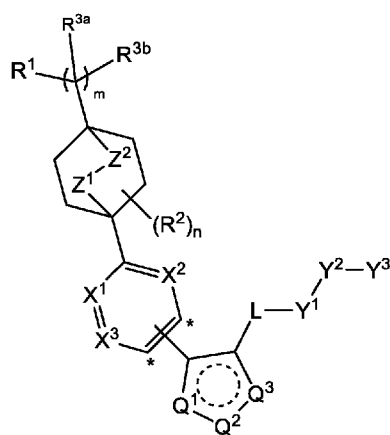
Declarations under Rule 4.17:

- 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))

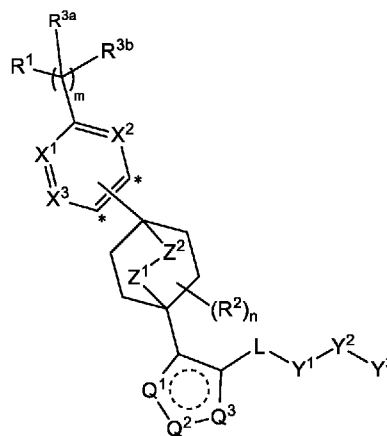
Published:

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

(54) Title: OXABICYCLO ACIDS AS LPA ANTAGONISTS



(Ia)



(Ib)

(57) Abstract: The present invention provides compounds of Formula (Ia) or (Ib) or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein all the variables are as defined herein. These compounds are selective LPA receptor inhibitors.

OXABICYCLO ACIDS AS LPA ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority benefit of U.S. Provisional Application No.
5 62/732,588, filed September 18, 2018; the entire content of which is herein incorporated
by reference.

FIELD OF THE INVENTION

The present invention relates to novel substituted oxabicyclo acid compounds,
10 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

Lysophospholipids are membrane-derived bioactive lipid mediators, of which one
15 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
phospholipids such as phosphatidylcholine (PC) or phosphatidic acid (PA).

20 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-
470-56905-4 & Zhao, Y. et al, *Biochim. Biophys. Acta (BBA)-Mol. Cell Biol. Of Lipids*,
25 **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
both eukaryotic and prokaryotic cells, but the LPAs have emerged only recently as
30 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). Recently it was reported that the LPA₁ receptor was over-expressed in idiopathic pulmonary fibrosis (IPF) patients. LPA₁ receptor knockout mice were also protected from bleomycin-induced lung fibrosis (Tager et al., *Nature Med.*, **2008**, 14, 45-54). LPA pathway inhibitors (e.g. an LPA₁ antagonist) were recently 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
5 fibrosis-diabetic nephropathy, systemic sclerosis-scleroderma, etc.).

SUMMARY OF THE INVENTION

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

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
15 pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts or solvates thereof.

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

20 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
25 least one symptom of the disease.

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
30 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), 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 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 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. 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 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.

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).

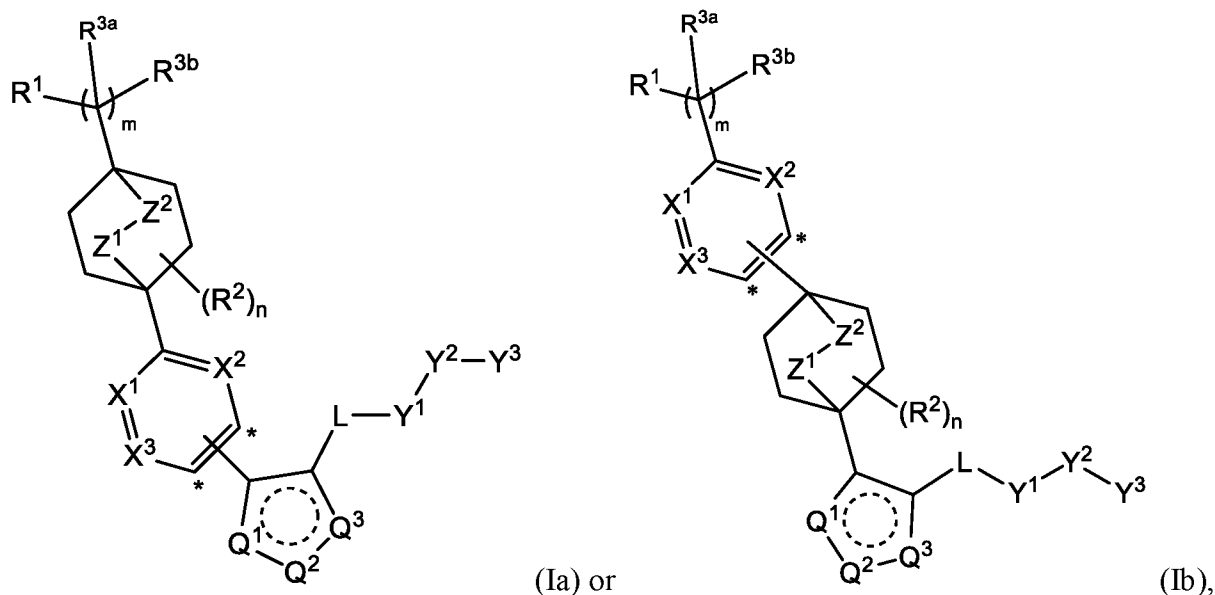
These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

In a 1st aspect, the present invention provides, *inter alia*, a compound of Formula

(Ia) or (Ib):

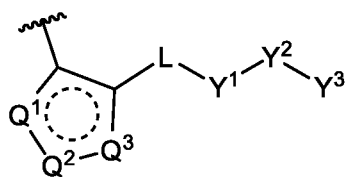


or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein:

one of Z^1 and Z^2 is O, and the other one is CH_2 ;

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

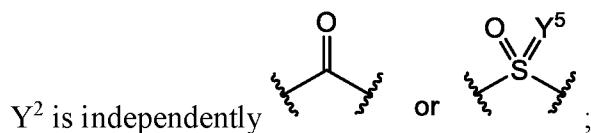
Q^1 , Q^2 , and Q^3 are independently N, O, NR^{5a} , or CR^{5b} , and the dashed circle denotes bonds forming an aromatic ring; provided that at least one of Q^1 , Q^2 , and Q^3 is not CR^{5b} ;



the moiety is attached to one of the two asterisk (*) positions in Formula (Ia) or (Ib);

L is independently a covalent bond or C_{1-4} alkylene substituted with 0 to 4 R^9 ;

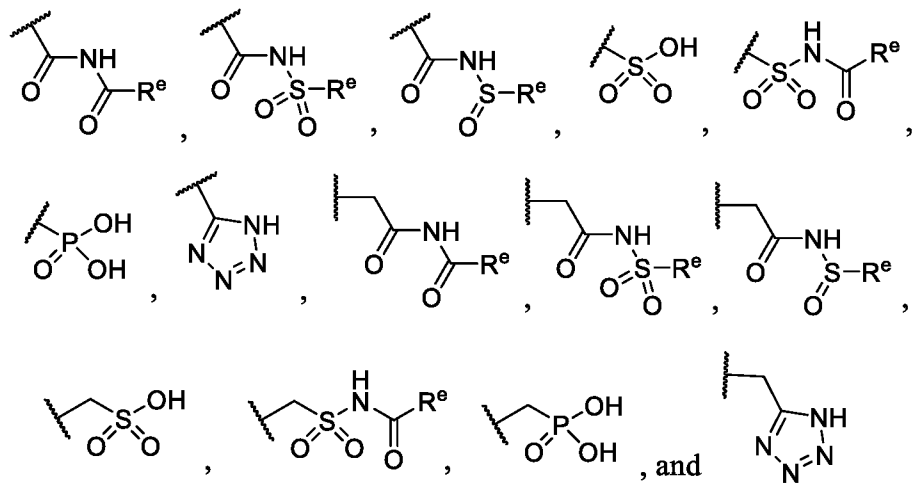
Y^1 is independently O or NR^7 ;



Y³ is independently OR⁴ or NR⁸R⁴, with the proviso that when Y¹ is O, then Y³ is not OR⁴;

Y⁵ independently is O or NH;

5 R¹ is independently cyano, -C(O)OR¹¹, -C(O)NR^{12a}R^{12b},



R² is each independently halo, cyano, hydroxyl, amino, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ alkylamino, -(CH₂)₀₋₁-(C₃₋₆ cycloalkyl), -(CH₂)₀₋₁-phenyl, or C₁₋₆ alkyl substituted with 0 to 3 R^c;

10 R^{3a} is independently hydrogen, halo, hydroxyl, or C₁₋₄ alkyl;

R^{3b} is independently hydrogen, halo, cyano, hydroxyl, amino, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy or C₁₋₆ alkyl substituted with 0 to 2 R^a;

or alternatively, R^{3a} and R^{3b} together, with the carbon atom they are attached to, form a C₃₋₄ carbocyclyl;

15 R⁴ is -L₁-R^{4a};

L₁ is independently a covalent bond or C₁₋₄ alkylene substituted with 0 to 4 R⁹;

R^{4a} is independently C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkenyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 3 to 8-membered heterocyclyl, 5 to 6-membered heteroaryl; wherein each of the alkyl, alkenyl, alkylene, cycloalkyl, aryl, heterocyclyl, and heteroaryl, by itself or as
20 part of other moiety, is independently substituted with 0 to 3 R¹⁰;

R^{5a} is independently hydrogen, C₁₋₄ haloalkyl, -(CH₂)₀₋₁-(C₃₋₆ cycloalkyl), -(CH₂)₀₋₁-phenyl, or C₁₋₆ alkyl substituted with 0 to 3 R^a;

R^{5b} is independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} alkylamino, $-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl), $-(CH_2)_{0-1}$ -phenyl, or C_{1-6} alkyl substituted with 0 to 3 R^b ;

R^6 is each independently hydrogen, halo, cyano, hydroxyl, amino,
 5 C_{1-4} alkylamino, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or C_{1-6} alkyl substituted with 0 to 1 R^b ;

R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl or C_{1-6} alkyl substituted with 0 to 1 R^c ;

R^9 is each independently halo, oxo, cyano, hydroxyl, amino, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, or C_{1-6} alkyl substituted with 0 to 3 R^a ;

R^{10} is each independently halo, hydroxyl, amino, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, phenyl, or 5 to 6 membered heteroaryl, C_{1-6} alkyl substituted with 0 to 3 R^b ;

R^{11} , R^{12a} and R^{12b} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or
 15 benzyl;

R^a is independently halo, cyano, hydroxyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

R^b is independently halo, cyano, hydroxyl, amino, C_{1-4} alkoxy, C_{1-4} haloalkyl, or
 20 C_{1-4} haloalkoxy;

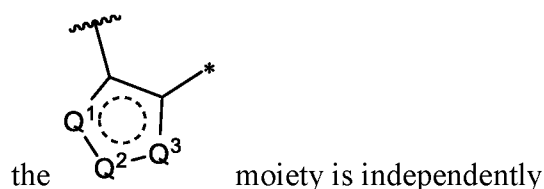
R^c is independently C_{1-4} haloalkyl, C_{3-6} cycloalkyl, or C_{1-6} alkyl substituted with 0 to 3 R^a ;

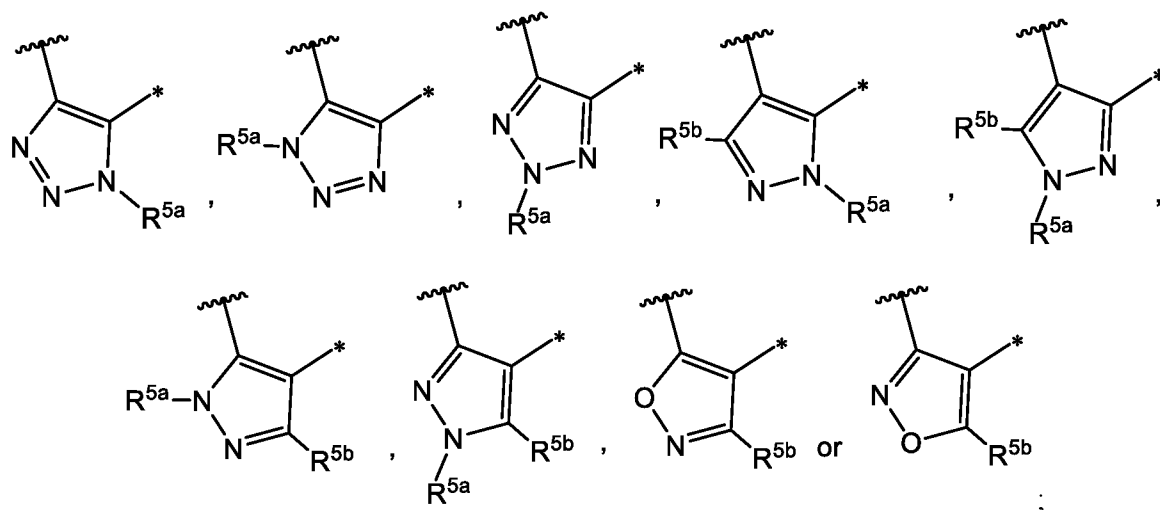
m is an integer of 0, 1, or 2; and

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

25 In one embodiment of Formula (Ia) or (Ib), within the scope of the 1st aspect, wherein X^1 , X^2 , and X^3 are CR^6 ; where R^6 is hydrogen, halo or C_{1-4} alkyl, e.g., methyl.

In a 2nd aspect, within the scope of the 1st aspect, wherein:





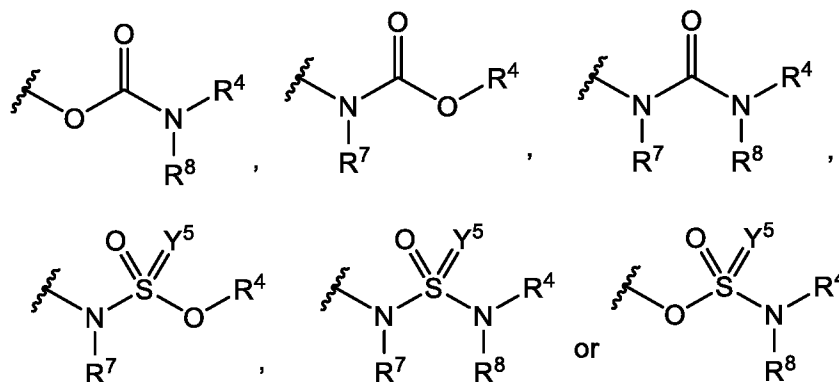
* denotes the attachment point to L; and

R^{5a} and R^{5b} are the same as defined in Claim 1.

5

In a 3rd aspect, within the scope of the 1st or 2nd aspect, wherein:

the $Y^1-Y^2-Y^3$ moiety is independently



10 In a 4th aspect, within the scope of any of the 1st to 3rd aspects, wherein L is a covalent bond or C_{1-2} alkylene.

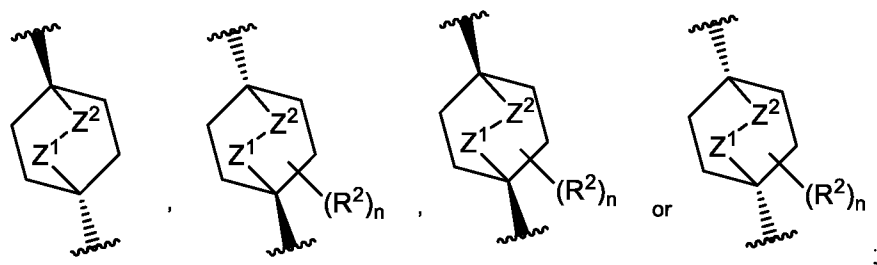
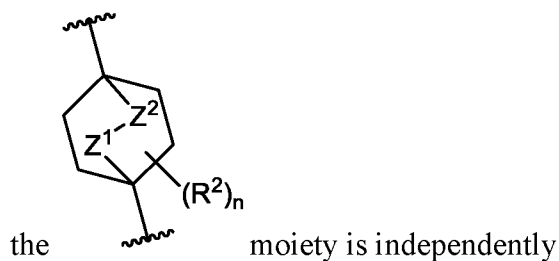
In one embodiment of Formula (Ia) or (Ib), within the scope of any of the 1st to 3rd aspects, wherein L is a covalent bond or methylene.

15 In a 5th aspect, within the scope of any of the 1st to 4th aspects, wherein X^1 , X^2 , and X^3 are independently CH or CR^{6a} , or one of X^1 , X^2 , and X^3 is N, and the remaining ones are CH or CR^{6a} ; and R^{6a} is independently halo, hydroxyl, C_{1-6} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

In a 6th aspect, within the scope of any of the 1st to 5th aspects, wherein R^{3a} and R^{3b} are independently hydrogen or C_{1-4} alkyl.

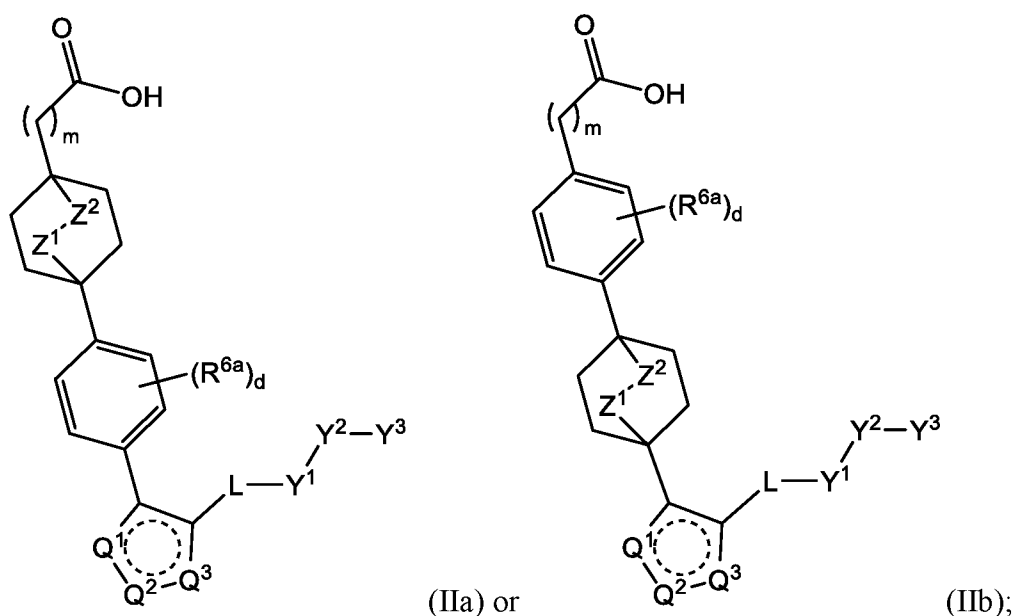
5 In a 7th aspect, within the scope of any of the 1st to 6th aspects, wherein R^1 is CO_2H .

In an 8th aspect, within the scope of any of the 1st to 7th aspects, wherein:



$-Z^1-Z^2-$ is $-O-CH_2-$ or $-CH_2-O-$; and
n is 0.

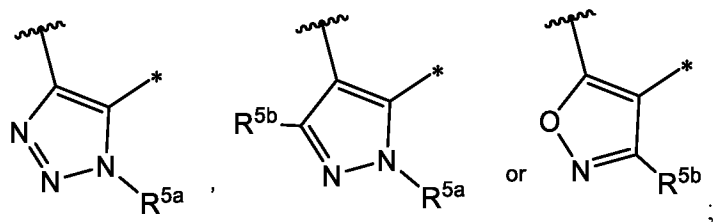
10 In a 9th aspect, the present invention provides a compound of Formula (IIa) or
15 (IIb):



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

$-Z^1-Z^2-$ is $-O-CH_2-$ or $-CH_2-O-$;

5 the moiety is independently

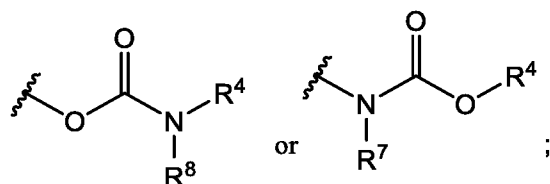


m is an integer of 1 or 2;

$*$ denotes the attachment point to L ;

L is independently a covalent bond or $-CH_2-$;

10 the moiety is independently



R^4 is independently C_{3-6} cycloalkyl, $-(CH_2)-C_{3-6}$ cycloalkyl,

-(CH(C₁₋₂ alkyl))-C₃₋₆ cycloalkyl, -(CH₂)-phenyl or -(CH(C₁₋₂ alkyl))-phenyl, wherein each of said cycloalkyl and phenyl is independently substituted with 0 to 3 R¹⁰;

R^{5a} is independently C₁₋₆ alkyl, or -CH₂-(C₃₋₆ cycloalkyl);

R^{5b} is independently hydrogen, halo, cyano, hydroxyl, C₁₋₄ alkyl, C₁₋₄ alkoxy,

5 C₁₋₄ haloalkyl, or C₁₋₄ haloalkoxy;

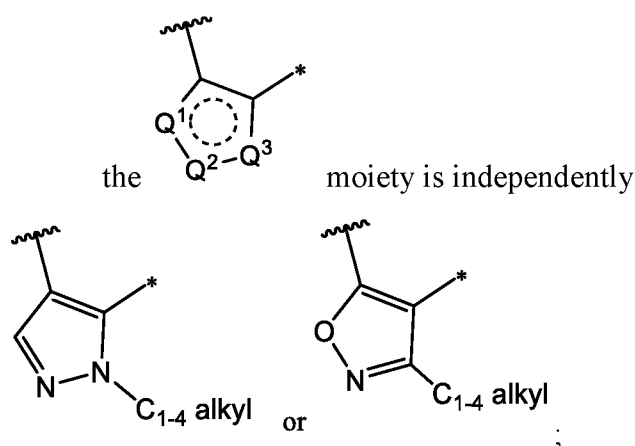
R^{6a} is each independently halo, hydroxyl, C₁₋₆ alkyl, C₁₋₄ haloalkyl, or C₁₋₄ alkoxy;

R⁷ and R⁸ are each independently hydrogen or C₁₋₂ alkyl;

R¹⁰ is each independently halo, cyano, hydroxyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkoxy; and

10 d is independently 0, 1 or 2.

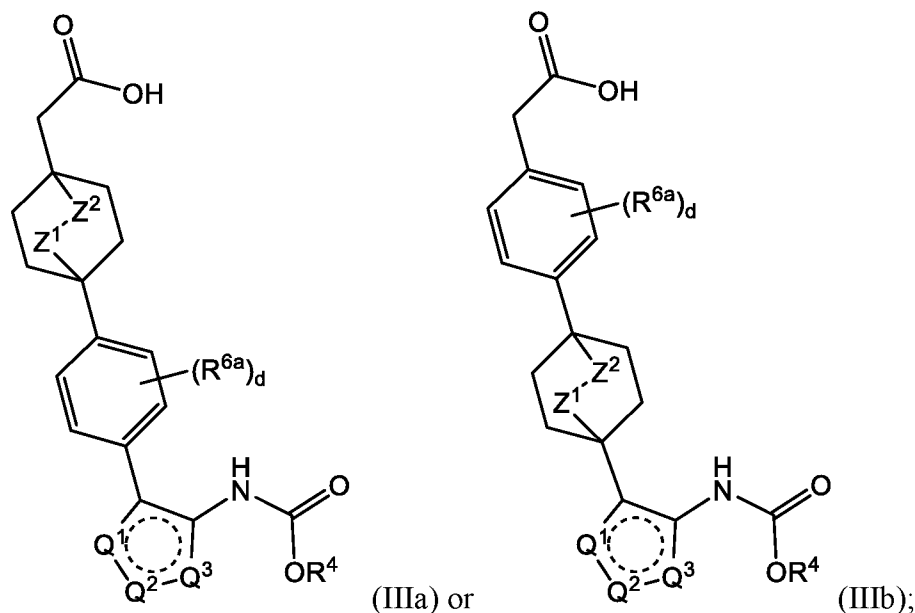
In a 10th aspect, within the scope of the 9th aspect, wherein:



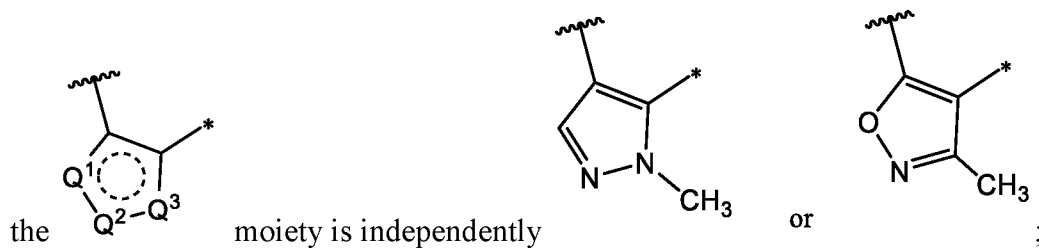
15 m is an integer of 1; and

R⁴ is independently -(CH₂)-C₃₋₆ cycloalkyl, -(CH(C₁₋₂ alkyl))-C₃₋₆ cycloalkyl, -(CH₂)-phenyl or -(CH(C₁₋₂ alkyl))-phenyl, wherein each of said cycloalkyl and phenyl is independently substituted with 0 to 2 R¹⁰.

20 In an 11th aspect, the present invention provides a compound of Formula (IIIa) or (IIIb):



wherein: $-Z^1-Z^2-$ is $-O-CH_2-$ or $-CH_2-O-$;



* denotes the attachment point to the nitrogen atom of $-NH-C(O)-OR^4$;

- 5 R^4 is independently $-(CH_2)$ -phenyl, or $-(CH(CH_3))$ -phenyl, wherein said phenyl is independently substituted with 0 to 2 R^{10} ;

R^{6a} is each independently halo or C_{1-4} alkyl;

R^{10} is each independently halo, cyano, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy; and

- 10 d is independently 0 or 1.

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.

- 15 In one embodiment, the compounds of the present invention have hLPA1 EC_{50} values ≤ 5000 nM, using the LPA1 functional antagonist assay; in another embodiment, the compounds of the present invention have hLPA1 EC_{50} values ≤ 1000 nM; in another embodiment, the compounds of the present invention have hLPA1 EC_{50} values ≤ 500 nM;

in another embodiment, the compounds of the present invention have hLPA1 EC₅₀ values ≤ 200 nM; in another embodiment, the compounds of the present invention have hLPA1 EC₅₀ values ≤ 100 nM; in another embodiment, the compounds of the present invention have hLPA1 EC₅₀ values ≤ 50 nM.

5

II. OTHER EMBODIMENTS OF THE INVENTION

In some embodiments, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is an antagonist of at least one LPA receptor. In some embodiments, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is an antagonist of LPA₁. In some embodiments, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is an antagonist of LPA₂. In some embodiments, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is an antagonist of LPA₃.

In some embodiments, presented herein are compounds selected from active metabolites, tautomers, pharmaceutically acceptable salts or solvates of a compound of the present invention.

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.

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.

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).

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.

In another embodiment, the present invention provides a method of treating a
5 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
embodiment of the method, the disease, disorder, or condition is related to pathological
10 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
(NASH), non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, diabetic
15 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,
spleen, small intestine, large intestine, stomach, testicle, or thyroid.

20 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
25 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-
30 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*

5 *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

10 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

15 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

20 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.*, 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.

30 "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-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,
 5 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 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
 10 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.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one
 15 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, 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-
 20 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
 25 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
 30 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(CH₂)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 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 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 C_{1-6} alkyl, the amino group can also be referred to as alkylamino. Examples of alkylamino group include, without limitation, methylamino, ethylamino, propylamino, isopropylamino and the like. In one embodiment, amino is $-NH_2$.

5 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-. “ C_1 to C_6 ” or “ C_{1-6} aminoalkyl” (or aminoalkyl), is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 aminoalkyl groups.

 The term “halogen” or “halo” as used herein alone or as part of another group
10 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 with one or more halogens. “ C_1 to C_6 haloalkyl” or “ C_{1-6} haloalkyl” (or haloalkyl), is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 haloalkyl groups. Examples of haloalkyl
15 include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include “fluoroalkyl” that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted
20 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 $CF_3CF_2CH_2$.

 “Haloalkoxy” or “haloalkyloxy” represents a haloalkyl group as defined above
25 with the indicated number of carbon atoms attached through an oxygen bridge. For example, “ C_1 to C_6 haloalkoxy” or “ C_{1-6} haloalkoxy”, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 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
30 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, CF₃CH₂O, CF₃O or CF₃CF₂CH₂O.

"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, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, 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
5 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
10 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.

20 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
25 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
30 group, refers to monocyclic or polycyclic (including bicyclic and tricyclic) aromatic

hydrocarbons, including, for example, phenyl, naphthyl, anthracenyl, and phenanthranyl. 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

5 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(CH₂)H, N(CH₃)₂,
10 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,
15 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)

20 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",

"heterocyclyl", or "heterocyclic group" includes non-aromatic ring systems, such as

25 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 or carbon atom that results in a stable structure. The heterocyclic rings described herein
30 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 heterocycle is not more than 1. Examples of heterocyclyl include, without limitation, azetidiny, piperaziny, piperidiny, piperidony, piperony, pyranyl, morpholinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, morpholinyl,

5 dihydrofuro[2,3-*b*]tetrahydrofuran.

As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is 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
10 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 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).

15 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 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
20 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-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

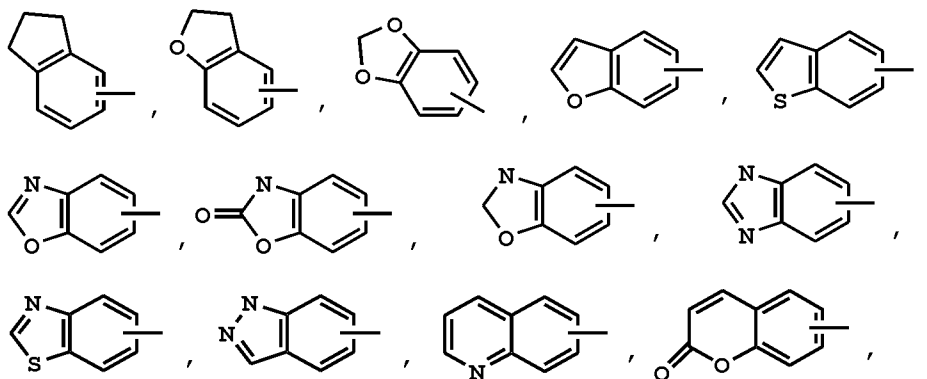
25 Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring.
30 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, 5 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 10 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, 15 benzisothiazolyl, benzimidazoliny, carbazolyl, 4*aH*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indoliziny, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, 20 isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, naphthyridinyl, 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, 25 purinyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinoliziny, quinoxaliny, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 30 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, isoxazolyl, oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, 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, 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,

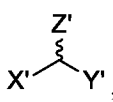


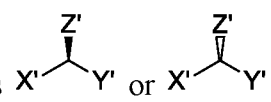
and may be optionally substituted through available carbon or nitrogen atoms (as applicable) with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, 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, heterocycloxy, 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

the enantiomers individually, such as , 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.

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.

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 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 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 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

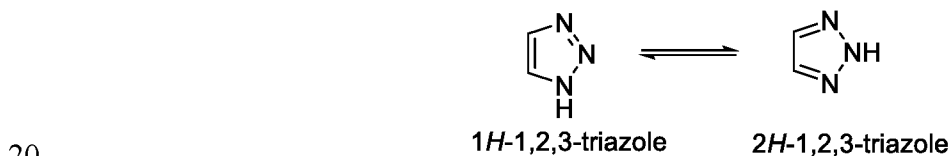
either carbon or heteroatom, are each independently replaced with one or more non-hydrogen substituent(s).

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 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 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 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*, 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 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, 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 the present invention, or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of the present invention which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate, nitrate
5 or acetate.

Preferred salts of the compounds of the present invention which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

In addition, compounds of the present invention may have prodrug forms. Any
10 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);
- 15 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
- 20 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
25 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 alkoxycarbonyloxy-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
30 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,
5 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).

10 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
15 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
20 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*.

25 "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.

The term "solvate" means a physical association of a compound of this invention
30 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 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, ethanlates, methanlates, and isopropanolates. Methods of solvation are generally known in the art.

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, "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 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
DEAD	Diethyl azodicarboxylate
Dess-Martin	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one
DIAD	Diisopropyl azodicarboxylate
DIBALH	Diisobutyl aluminum hydride
DIC or DIPCDI	diisopropylcarbodiimide

DIEA, DIPEA or Hunig's base	diisopropylethylamine
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-imidazolidinyldene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium
HCl	hydrochloric acid
HATU	O-(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HEPES	4-(2-hydroxyethyl)piperaxine-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), 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.

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.

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 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) inhibition/activation, phospholipase C (PLC) activation/Ca²⁺ 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-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 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-arachidonoyl (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).

5 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
10 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
15 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
20 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 G_{12/13}-Rho signaling
25 pathways and is expressed in the inner root sheaths of human hair follicles.

Illustrative Biological Activity

Wound Healing

Normal wound healing occurs by a highly coordinated sequence of events in
30 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 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 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 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 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 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

5 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
10 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
15 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
20 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.
25 Kantarci, *et al.*, *J. Pathol.* 210 (2006) 59–66).

LPA is associated with the progression of liver fibrosis. *In vitro*, LPA induces 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
30 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 (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).

5 LPA is associated with heart disease and myocardial remodeling. Serum LPA 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).

10 **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.

15 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
20 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
25 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 bleomycin challenge with reduced fibroblast accumulation and vascular leakage. In human subjects with IPF, high LPA levels were observed in bronchoalveolar lavage
30 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, 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 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 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.

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**, 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. UUO 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. 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. UUO 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 in the expression of the profibrotic cytokine CTGF. CTGF plays a crucial role in UUO-induced tubulointerstitial fibrosis (TIF), and is involved in the profibrotic activity of TGF β . 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.

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 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 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 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 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 the present invention, or a pharmaceutically acceptable salt thereof, is used to treat or prevent fibrosis in a mammal. In one aspect, a compound of Formulas (I), or a pharmaceutically acceptable salt 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 amount of a compound of Formulas (I), or a pharmaceutically acceptable salt 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 a genetic predisposition of developing fibrosis of an organ or tissue. In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt 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 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 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 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 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

5 hepatitis; Head and neck fibrosis, *e.g.*, radiation induced; Corneal scarring, *e.g.*, LASIK (laser-assisted in situ keratomileusis), corneal transplant, and trabeculectomy; 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

10 connective tissue disease, and Peyronie's disease.

In one aspect, a mammal suffering from one of the following non-limiting exemplary diseases, disorders, or conditions will benefit from therapy with a compound of the present invention, or a pharmaceutically acceptable salt thereof: atherosclerosis, thrombosis, heart disease, vasculitis, formation of scar tissue, restenosis, phlebitis, COPD

15 (chronic obstructive pulmonary disease), pulmonary hypertension, pulmonary fibrosis, pulmonary inflammation, bowel adhesions, bladder fibrosis and cystitis, fibrosis of the nasal passages, sinusitis, inflammation mediated by neutrophils, and fibrosis mediated by fibroblasts.

In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is administered to a mammal with fibrosis of an organ or tissue or

20 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 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

25 more agents include uteroglobin.

In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used to treat a dermatological disorders in a mammal. The term “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

30 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

Syndrome, urticaria. In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used to treat systemic sclerosis.

Pain

5 Since LPA is released following tissue injury, LPA₁ plays an important role in the 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
10 downstream Rho–ROCK activation play a role in the initiation of neuropathic pain 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
15 observed in LPA₁-null mice or AS-ODN injected wild-type mice. LPA signaling appears 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).

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

Cancer

Lysophospholipid receptor signaling plays a role in the etiology of cancer.
30 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 μ M) in the ascitic fluid of ovarian cancer patients. Ovarian cancer cells constitutively produce increased amounts of LPA as compared to 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 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 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).

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-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 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 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 the present invention inhibits or reduces IL-8 expression in ovarian cancer cell lines.

In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used in the treatment of cancer. In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used in the treatment of malignant and benign proliferative disease. In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically acceptable salt 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 cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver)

cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell

5 leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt 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

10 lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive

15 neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sézary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma,

20 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

25 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.

30

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 hyper-responsiveness 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 the present invention, or a pharmaceutically acceptable salt thereof, is used in the treatment of various allergic disorders in a mammal. In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt

thereof, is used in the treatment of respiratory diseases, disorders or conditions in a mammal. In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used in the treatment of asthma in a mammal. In one aspect, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used
5 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
10 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
15 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
20 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 the present invention, or a pharmaceutically acceptable salt thereof, in the treatment or prevention of chronic obstructive pulmonary disease in a mammal comprising administering to the mammal at
25 least once an effective amount of at least one compound of the present invention, or a pharmaceutically acceptable salt 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.

30 **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

5 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).

15 In one aspect, provided is a compound of the present invention, or a pharmaceutically acceptable salt 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, 20 those found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as degenerative disk disease and sciatica.

In one aspect, provided is a compound of the present invention, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a CNS 25 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, post-surgical cognitive dysfunction, migraine, peripheral neuropathy/neuropathic pain, spinal cord injury, cerebral edema and head injury.

30

Cardiovascular Disorders

Cardiovascular phenotypes observed after targeted deletion of lysophospholipid 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.

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 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 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 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 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 the present invention, or a pharmaceutically acceptable salt thereof, is used to treat or prevent cardiovascular disease in mammal.

The term “cardiovascular disease,” as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia (atrial or
5 ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood
10 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 infarction, aortic aneurysm, vasculitis and stroke comprising administering at least once
15 to the mammal an effective amount of at least one compound of the present invention, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition or medicament which includes a compound of the present invention, or a pharmaceutically acceptable salt thereof.

In one aspect, provided herein are methods for reducing cardiac reperfusion injury
20 following myocardial ischemia and/or endotoxic shock comprising administering at least once to the mammal an effective amount of at least one compound of the present invention, or a pharmaceutically acceptable salt 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
25 amount of at least one compound of the present invention, or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically
30 acceptable salt 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 the present invention, or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically acceptable salt 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, 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, 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 the present invention, or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject already has a LPA-dependent or LPA-mediated disease or condition at the time of administration, or is at risk of developing a LPA-dependent or LPA-mediated disease or condition.

5 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 the present invention, or a pharmaceutically acceptable salt 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
10 indirectly modulated, including reducing and/or inhibiting, by the administration of (at least once) a therapeutically effective amount of at least one compound of the present invention, or a pharmaceutically acceptable salt thereof. Such modulation includes, but is not limited to, reducing and/or inhibiting the amount and/or activity of a LPA receptor. In one aspect, the LPA receptor is LPA₁.

15 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, LPA contracts the urinary tract and prostate *in vitro* and increases intraurethral pressure *in vivo* (WO 02/062389).

20 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 the present invention, or a pharmaceutically acceptable salt thereof.

25 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 the present invention, or a pharmaceutically acceptable salt thereof.

 In accordance with one aspect, methods described herein include the diagnosis or
30 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 the present invention, or a pharmaceutically acceptable salt thereof, and determining whether or not the patient responds to the treatment.

In one aspect provided herein are compounds of the present invention, pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and
5 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
10 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
15 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 the present invention, or a pharmaceutically
20 acceptable salt 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.

In one aspect, presented herein is the use of a compound of the present invention,
25 or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically acceptable salt thereof.

30 In one aspect, presented herein is the use of a compound of the present invention, or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically acceptable salt thereof.

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 the present invention, or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically acceptable salt thereof.

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 the present invention, or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically acceptable salt thereof.

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 the present invention, or a pharmaceutically acceptable salt 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 the present invention, or a pharmaceutically acceptable salt thereof.

a. In Vitro Assays

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, 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# 14025-092), 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 μ M. 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. 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

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 μ g/ μ L). Exactly 2 minutes following the LPA challenge, the mice are euthanized by decapitation and the trunk blood is collected. These samples are collectively centrifuged and individual 75 μ L 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).

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 μ g/ μ 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.

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

In some embodiments, provided is a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention, or a

pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition 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 the present invention, or a

5 pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient. In one aspect, the pharmaceutical composition is formulated for intravenous 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
10 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.

In some embodiments, the pharmaceutical composition further comprises one or more additional therapeutically active agents selected from: corticosteroids (*e.g.*,

15 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), leukotriene formation inhibitors, monoacylglycerol kinase inhibitors, phospholipase A₁ inhibitors, phospholipase A₂ inhibitors, and lysophospholipase D (lysoPLD) inhibitors,
20 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
25 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
30 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, obeticholic acid, aramchol, GFT-505, eicosapentaenoic acid ethyl ester, metformin, metreleptin, muromonab-CD3, oltipraz, IMM-124-E, MK-4074, PX-102, RO-5093151.

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

In some embodiments, the one or more additional therapeutically active agents other than a compound of the present invention, or a pharmaceutically acceptable salt thereof, are selected from: corticosteroids (e.g., dexamethasone or fluticasone),

15 immunosuppressants (e.g., tacrolimus & pimecrolimus), analgesics, anti-cancer agent, anti-inflammatories, chemokine receptor antagonists, bronchodilators, leukotriene receptor antagonists (e.g., montelukast or zafirlukast), leukotriene formation inhibitors, monoacylglycerol kinase inhibitors, phospholipase A₁ inhibitors, phospholipase A₂

20 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

25 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).

30 In some embodiments, the one or more additional therapeutically active agents other than a compound of the present invention, or a pharmaceutically acceptable salt 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,

5 obeticholic acid, aramchol, GFT-505, eicosapentyl ethyl ester, metformin, metreleptin, muromonab-CD3, oltipraz, IMM-124-E, MK-4074, PX-102, RO-5093151.

In some embodiments, the one or more additional therapeutically active agents other than a compound of the present invention, or a pharmaceutically acceptable salt thereof, are selected from ACE inhibitors, ramipril, AII antagonists, irbesartan, anti-

10 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

15 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,

20 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 the present invention, or a pharmaceutically acceptable salt thereof, are selected from Gremlin-1 mAb, PA1-1 mAb, Promedior (PRM-151; recombinant human Pentraxin-2); FGF21, TGF β antagonists, α v β 6 & α v β pan-

25 antagonists; FAK inhibitors, TG2 inhibitors, LOXL2 inhibitors, NOX4 inhibitors, MGAT2 inhibitors, GPR120 agonists.

Pharmaceutical formulations described herein are administrable to a subject in a

30 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 release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile
5 release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

In some embodiments, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is administered orally.

In some embodiments, the compound of the present invention, or a
10 pharmaceutically acceptable salt thereof, is administered topically. In such embodiments, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is 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
15 contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. In one aspect, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is administered topically to the skin.

In another aspect, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is administered by inhalation. In one embodiment, the compound
20 of the present invention, or a pharmaceutically acceptable salt thereof, is administered by inhalation that directly targets the pulmonary system.

In another aspect, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is formulated for intranasal administration. Such formulations include nasal sprays, nasal mists, and the like.

25 In another aspect, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is formulated as eye drops.

In another aspect is the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease, disorder or conditions in which the activity of at least one LPA receptor
30 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.

In any of the aforementioned aspects are further embodiments in which: (a) the effective amount of the compound of the present invention, or a pharmaceutically acceptable salt 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 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; 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 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) 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 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

the present invention or a pharmaceutically acceptable salt thereof to the mammal in 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
5 of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

In some cases disclosed herein is the use of a compound of the present invention, or a pharmaceutically acceptable salt 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 the present invention,
10 or a pharmaceutically acceptable salt thereof, in the treatment or prevention of a LPA-dependent or LPA-mediated disease or condition.

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 the present invention, or a pharmaceutically
15 acceptable salt thereof.

In one aspect, LPA-dependent or LPA-mediated diseases or conditions include, 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
20 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 respiratory disease or condition. In some embodiments, the respiratory disease or
25 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 different etiologies including iatrogenic drug-induced fibrosis, occupational and/or
30 environmental induced fibrosis, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, alveolar proteinosis, langerhans cell granulomatosis, lymphangioleiomyomatosis, inherited diseases (Hermansky-Pudlak

Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial 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 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; 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.

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 the present invention or a pharmaceutically acceptable salt thereof to a mammal in need thereof.

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

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

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

proteinosis, langerhans cell granulomatosis, lymphangiomyomatosis, Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease.

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

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

10 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 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.

15 In any of the aforementioned aspects involving the treatment of LPA dependent 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 the present invention, or a pharmaceutically acceptable salt thereof. In various embodiments, each agent is administered in any order, including simultaneously.

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

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

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
25 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. 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.

30 Articles of manufacture, which include packaging material, a compound of the present invention, or a pharmaceutically acceptable salt thereof, within the packaging 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 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 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 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.

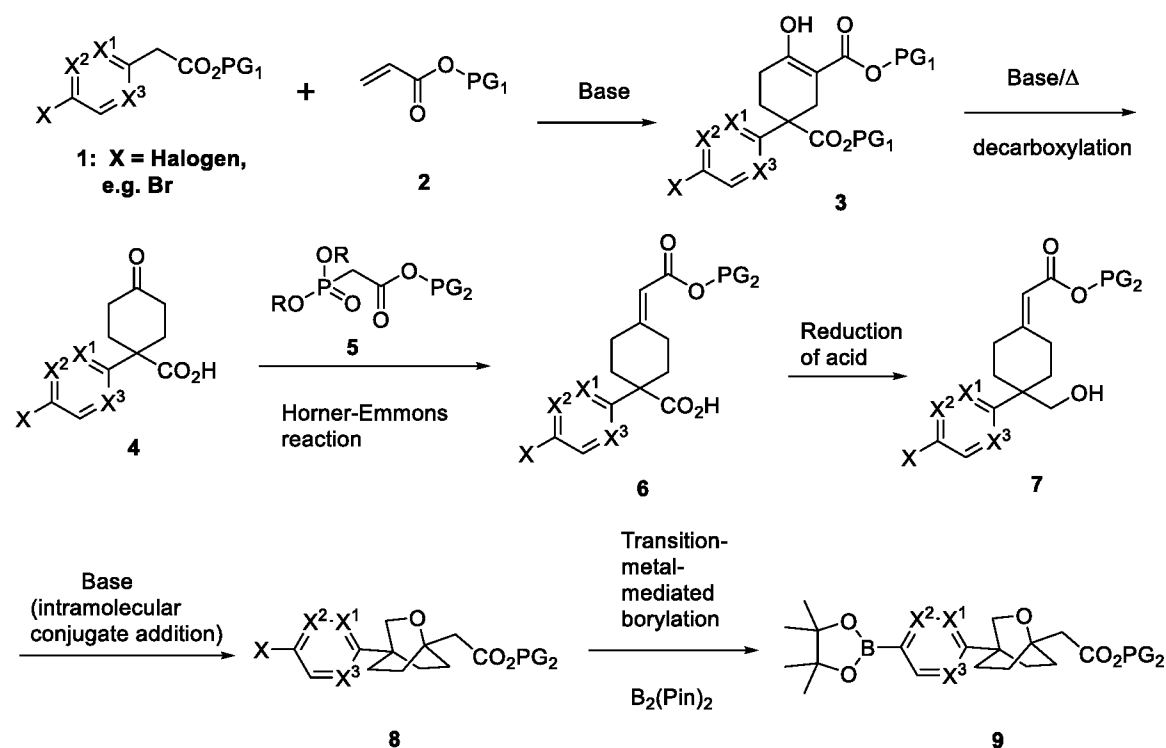
It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing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

The compounds of the present invention 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.

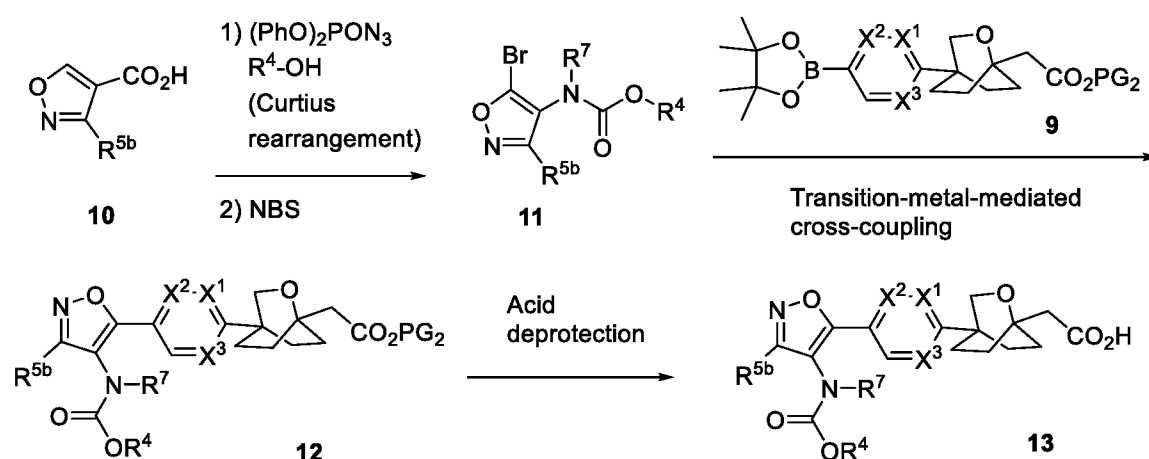
- 10 Scheme 1 describes the synthesis of pinacol boronate 9. A double Michael reaction of the anion of a 4-halo- (preferably 4-bromo-) phenyl acetic acid ester 1 with acrylate ester 2 (two equivalents) provides the β -keto cyclohexyl ester 3. Hydrolysis of diester 3 followed by decarboxylation of the β -keto cyclohexyl acid intermediate furnishes the cyclohexyl keto-acid 4. Horner-Emmons reaction with phosphonate-ester 5
- 15 provides the α,β -unsaturated ester-acid 6. Reduction of the acid moiety of ester-acid 6 furnishes the cyclohexyl alcohol 7, which undergoes a base-mediated intramolecular oxy-Michael reaction to provide the oxabicyclo[2.2.2] ester 8. Reaction of the haloarene 8 with bis(pinacolato)diboron in the presence of an appropriate transition metal catalyst (e.g. palladium, for instance Ishiyama, T. et al, *J. Org. Chem.* **1995**, 60, 7508-7510) provides
- 20 the corresponding pinacol boronate 9.

Scheme 1



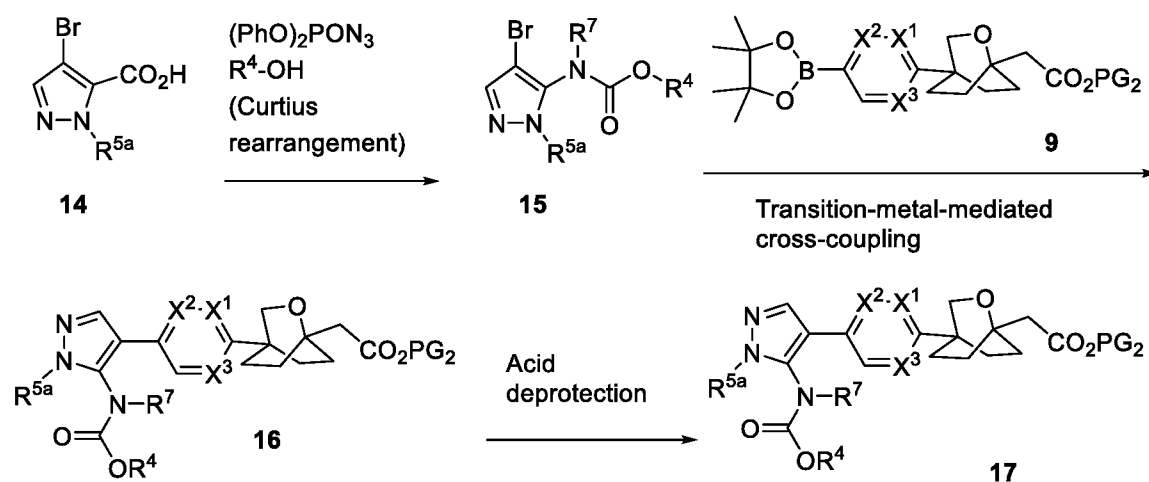
Scheme 2 describes the synthesis of isoxazole 2-oxabicyclo[2.2.2]octan-1-yl aryl acetic acids 13. Isoxazole carboxylic acid 10 is subjected to a Curtius rearrangement with $(PhO)_2PON_3$ in the presence of an appropriate alcohol to give the corresponding isoxazole N-carbamate, which is then brominated (e.g. N-bromo-succinimide) to provide the bromo-isoxazole N-carbamate 11. Suzuki-Miyaura cross coupling of aryl boronate 9 and the bromo-isoxazole 11 furnishes the aryl isoxazole N-carbamate 12, which is then deprotected to provide the desired oxabicyclo[2.2.2] isoxazole N-carbamate acids 13.

Scheme 2



Scheme 3 describes the analogous synthesis of pyrazole 2-oxabicyclo[2.2.2]octan-1-yl acetic acids 17. 4-Bromo-pyrazole-5-carboxylic acid 14 is subjected to a Curtius rearrangement with $(\text{PhO})_2\text{PON}_3$ in the presence of an appropriate alcohol to provide the corresponding bromo-pyrazole-N-carbamate 15. Suzuki-Miyaura cross coupling of aryl boronate 9 and the bromo-pyrazole 15 furnishes the aryl pyrazole N-carbamate 16, which is then deprotected to provide the desired oxabicyclo[2.2.2] pyrazole N-carbamate acids 17.

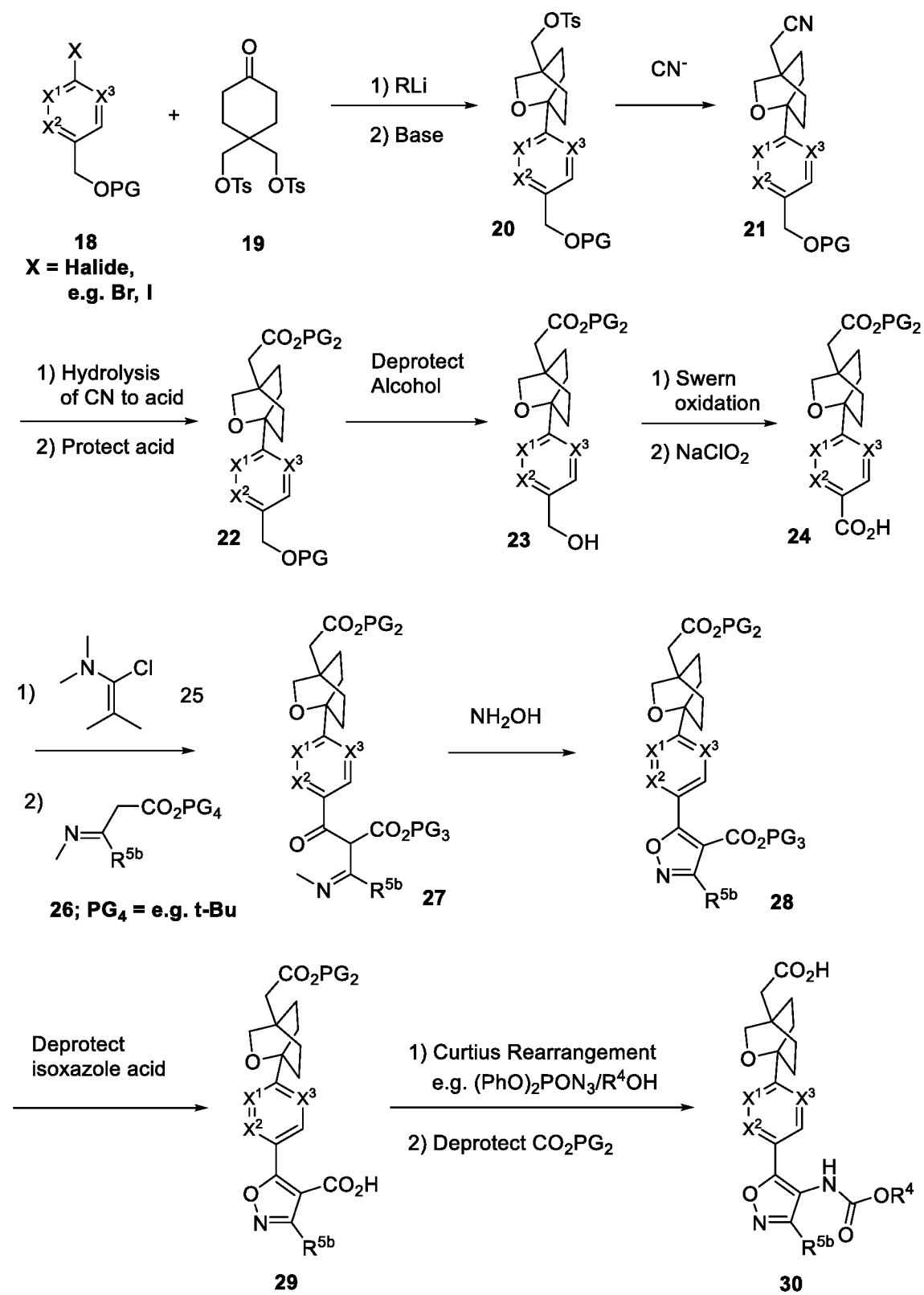
Scheme 3



Scheme 4 describes the synthesis of the regioisomeric isoxazole oxabicyclo[2.2.2] aryl acetic acids 30. An appropriately protected halo-benzyl alcohol 18 is lithiated (e.g. with $n\text{-BuLi}$) and reacted with the 4-oxocyclohexanone bis-tosylate 19

(synthesized from from diethyl malonate and ethyl acrylate in 6 steps, as described in WO 2001034610) to furnish the corresponding aryl cyclohexanol bis-tosylate adduct, which is then subjected to base-mediated intramolecular displacement of a tosylate by the alcohol to provide the oxabicyclo[2.2.2]tosylate 20. Displacement of tosylate 20 by cyanide provides nitrile 21, which is subjected to hydrolysis to give the corresponding acid, which is then appropriately protected (with an orthogonal protecting group to the benzylic alcohol) as oxabicyclic ester 22. Selective deprotection of the benzylic alcohol (23) followed by oxidation (e.g., Swern oxidation or Dess-Martin periodinane followed by NaClO₂ oxidation to the acid, e.g. Lindgren, B. O., *Acta Chem. Scand.* **1973**, 27, 888) provides the benzoic acid 24. Benzoic acid 24 is treated with Vilsmeier reagent 25 to give the acid chloride, which is then reacted with an appropriate (E)-3-(methyl-imino)butanoate ester 26, to give the corresponding β -keto-imine ester 27. The β -keto-imine ester 27 is reacted with hydroxylamine to provide the phenyl isoxazole ester 28 (Ishiyama, T., et al., *J. Org. Chem.* **1995**, 60, 7508). Deprotection of the isoxazole ester 28 provides the isoxazole acid 29, which is then subjected to a Curtius rearrangement and reaction with an appropriate alcohol to provide the corresponding isoxazole carbamate. Final deprotection of the isoxazole carbamate-oxabicyclic ester provides the desired isoxazole oxabicyclic[2.2.2] N-carbamate acetic acids 30.

Scheme 4



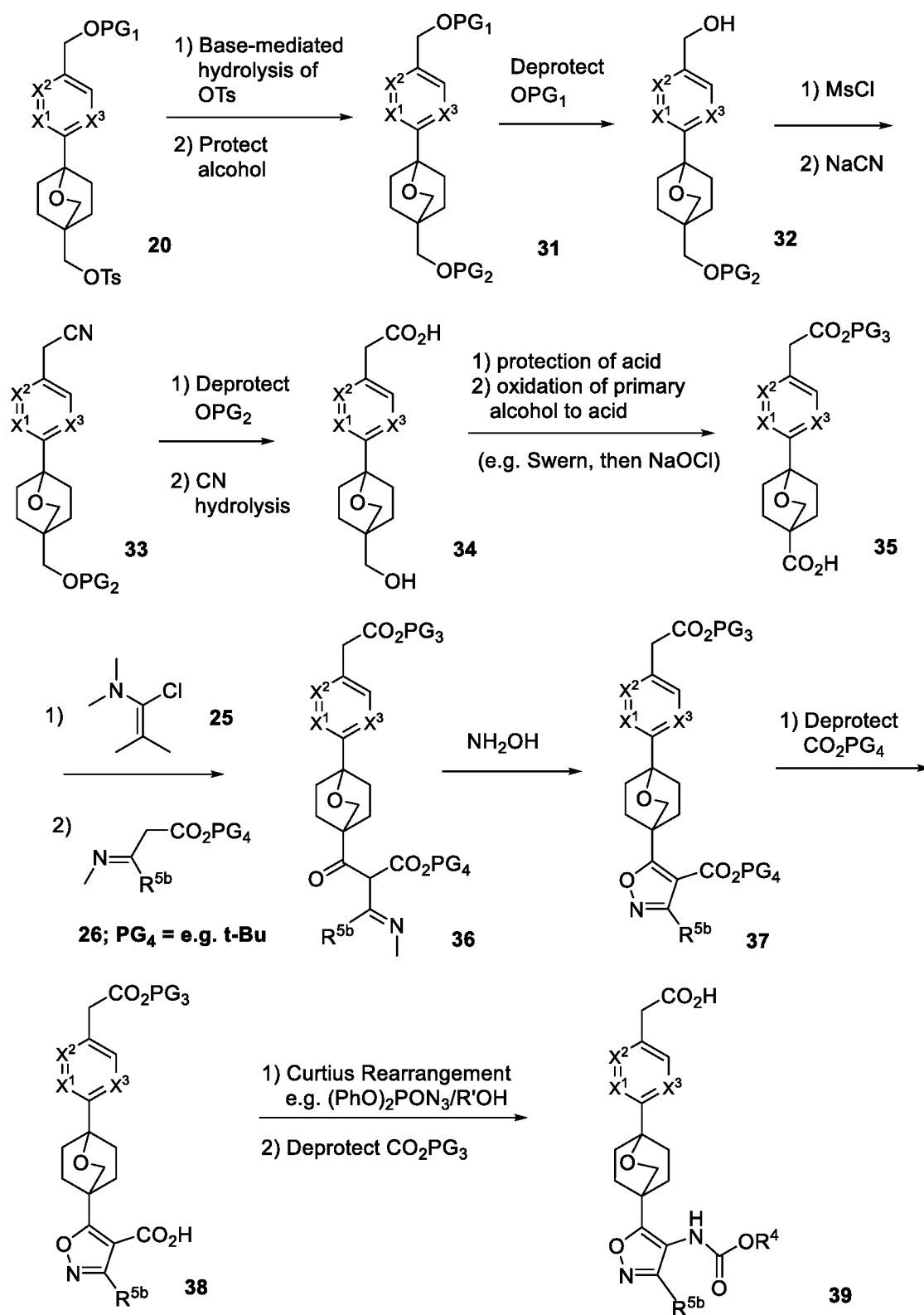
Scheme 5 describes the synthesis of oxabicyclo[2.2.2]octan-1-yl acetic acids 39. Tosylate 20 is hydrolyzed and protected (orthogonally from the other primary alcohol) as 31. Deprotection of the benzylic alcohol of 31 provides 32, which is then converted to the corresponding mesylate and displaced with cyanide to provide benzylic nitrile 33.

5 Deprotection of the alcohol and nitrile hydrolysis provide the phenylacetic acid alcohol 34. Protection of the phenylacetic acid, followed by oxidation of the primary alcohol (e.g., Swern oxidation or Dess-Martin periodinane followed by NaClO₂ oxidation to the acid, e.g. Lindgren, B. O., *Acta Chem. Scand.* **1973**, 27, 888) provides the acid-ester 35. The acid 35 is treated with Vilsmeier reagent 25 to give the acid chloride, which is then

10 reacted with an appropriate (E)-3-(methyl-imino) butanoate ester 26, to give the corresponding β -keto-imine ester 36. The β -keto-imine ester 36 is reacted with hydroxylamine to provide the isoxazole ester 37 (Ishiyama, T., et al., *J. Org. Chem.* **1995**, 60, 7508). Deprotection of the isoxazole ester 37 provides the isoxazole acid 38, which is then subjected to a Curtius rearrangement and reaction with an appropriate alcohol to

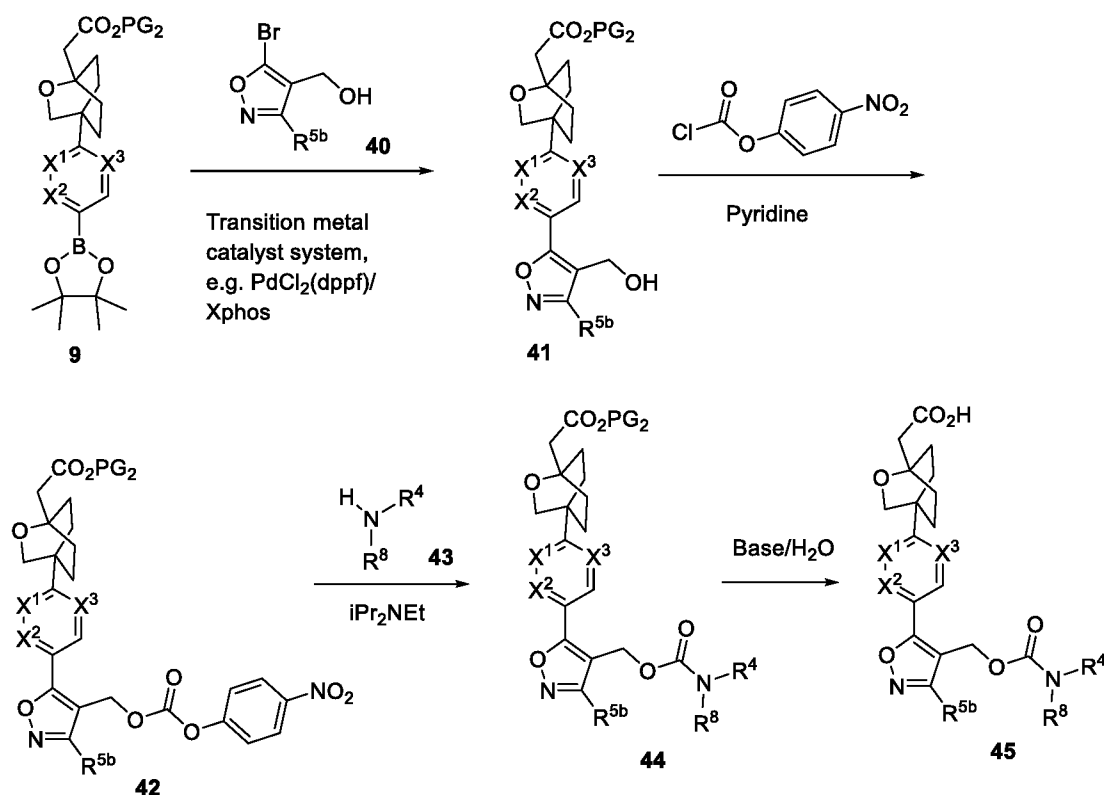
15 provide the corresponding isoxazole carbamate. Final deprotection of the isoxazole carbamate phenylacetic acid ester provides the desired oxabicyclo[2.2.2]octan-1-yl acetic acids 39.

Scheme 5



Scheme 6 describes the synthesis of isoxazole O-carbamyl oxabicyclo[2.2.2]octan-1-yl acetic acids 45. Cross-coupling (under standard transition metal-catalyzed conditions, e.g. PdCl₂(dppf)/Xphos) of the oxabicyclo[2.2.2] acetic ester boronate 9 with 5-bromo-3-methyl-isoxazol-4-yl)methanol provides the aryl isoxazole alcohol 41. Reaction of isoxazole alcohol 41 with 4-nitrophenyl chloroformate provides the intermediate isoxazole 4-nitrophenyl carbonate 42, which is then reacted with amine 43 to provide the isoxazole O-carbamate 44. Hydrolysis of the oxabicyclo[2.2.2] acetic ester 44 provides the desired isoxazole O-carbamyl oxabicyclo [2.2.2]octan-1-yl acetic acids 45.

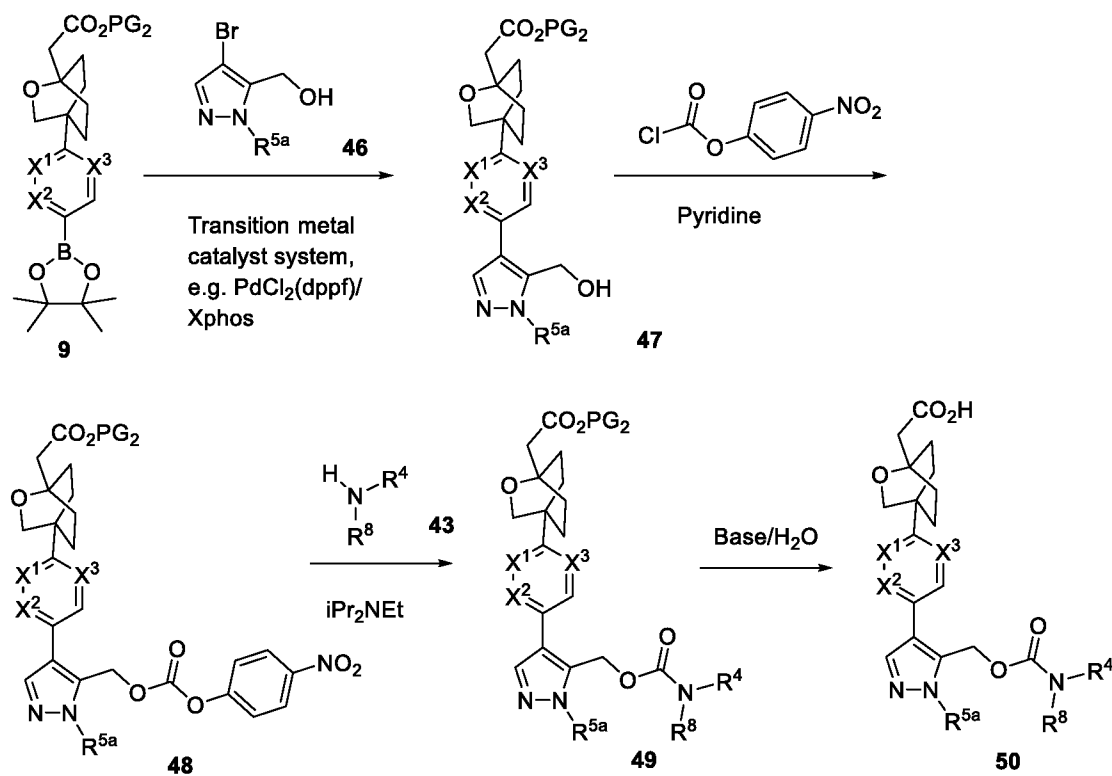
Scheme 6



Scheme 7 describes the synthesis of pyrazole O-carbamyl oxabicyclo[2.2.2]octan-1-yl acetic acids 45. Cross-coupling (under standard transition metal-catalyzed conditions, e.g. PdCl₂(dppf)/Xphos) of the oxabicyclo[2.2.2] acetic ester boronate 9 with (4-bromo-1-methyl-1H-pyrazol-5-yl)methanol 46 provides the aryl pyrazole alcohol 47. Reaction of pyrazole alcohol 47 with 4-nitrophenyl chloroformate provides the intermediate pyrazole 4-nitrophenyl carbonate 48, which is then reacted with amine 43 to

provide the pyrazole O-carbamate 49. Hydrolysis of the oxabicyclo[2.2.2] acetic ester 49 provides the desired pyrazole O-carbamyl oxabicyclo[2.2.2] octan-1-yl acetic acids 50.

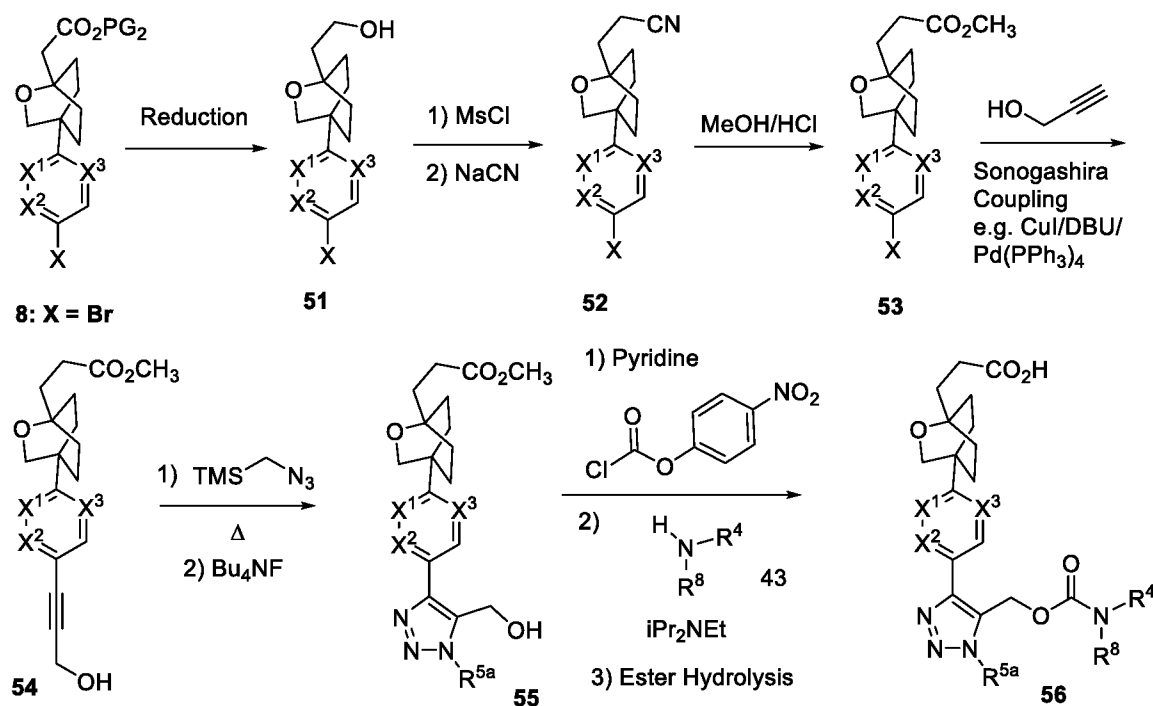
Scheme 7



Scheme 8 describes the synthesis of triazole O-carbamyl oxabicyclo[2.2.2]octan-1-yl propanoic acids 56. Reduction of oxabicyclo[2.2.2] acetic acid ester 8 (with e.g. DIBALH) provides the alcohol 51, which is converted (via the corresponding mesylate and displacement with NaCN) to the corresponding nitrile 52. Hydrolysis of the nitrile in the presence of methanol provides the corresponding methyl ester 53. Sonogashira coupling reaction (e.g. Alper, P. et al, WO 2008097428) of oxabicyclo[2.2.2] aryl halide 53 with propargyl alcohol furnishes the aryl propargyl alcohol 54. Reaction of propargyl alcohol 54 with trimethylsilyl methyl azide (Qian, Y. et al, *J. Med. Chem.*, **2012**, 55, 7920-7939) under either thermal or transition-metal catalyzed conditions (Boren, B.C. et al., *J. Am. Chem. Soc.*, **2008**, 130, 8923-8930) provides the silylated 1,2,3 triazole; the trimethylsilyl group is subsequently removed under standard desilylation conditions (e.g. Bu₄NF, as in Qian, Y. et al, *J. Med. Chem.*, **2012**, 55, 7920-7939) to give the triazole alcohol 55. Reaction of triazole alcohol 55 with 4-nitrophenyl chloroformate provides the

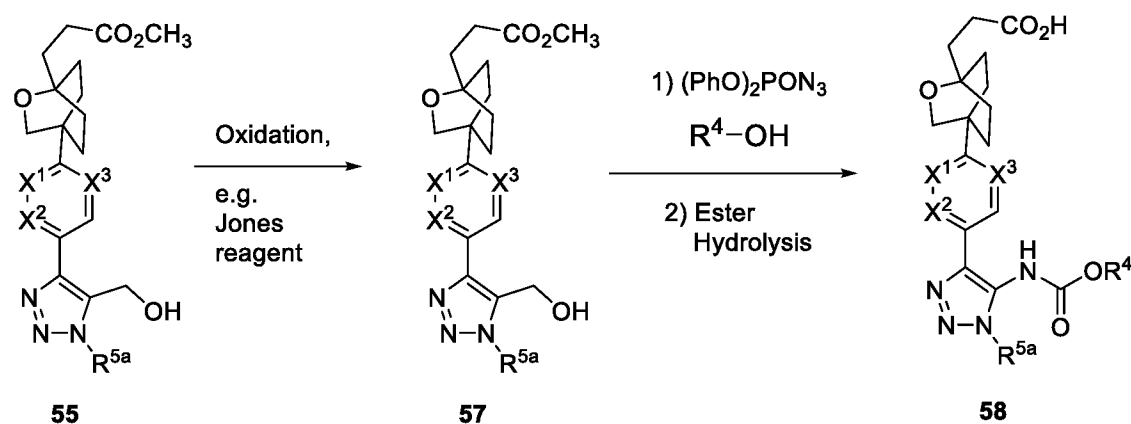
intermediate triazole 4-nitrophenyl carbonate, which is then reacted with amine 43 followed by ester hydrolysis to provide the desired triazole O-carbamyl oxabicyclo[2.2.2]octan-1-yl propanoic acids 56.

5 Scheme 8



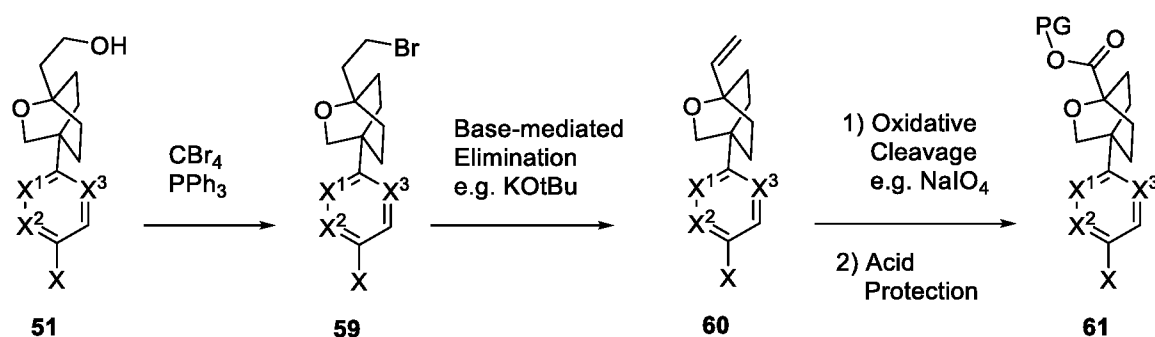
Scheme 9 describes the synthesis of triazole N-carbamyl oxabicyclo[2.2.2]octan-1-yl propanoic acids 58. Oxidation of triazole alcohol 55 provides the triazole acid 57 (e.g. via direct oxidation to the acid with Jones reagent/pyridinium dichromate or via a 2-step procedure via the aldehyde [Swern oxidation or Dess-Martin periodinane followed by NaClO₂ oxidation to the acid, e.g. Lindgren, B. O., *Acta Chem. Scand.* **1973**, 27, 888]). Curtius rearrangement of triazole acid 57 in the presence of an alcohol R₁-OH provides the triazole NH-carbamate, which is subjected to ester hydrolysis to provide the desired triazole N-carbamyl oxabicyclo[2.2.2]octan-1-yl propanoic acids 58.

Scheme 9



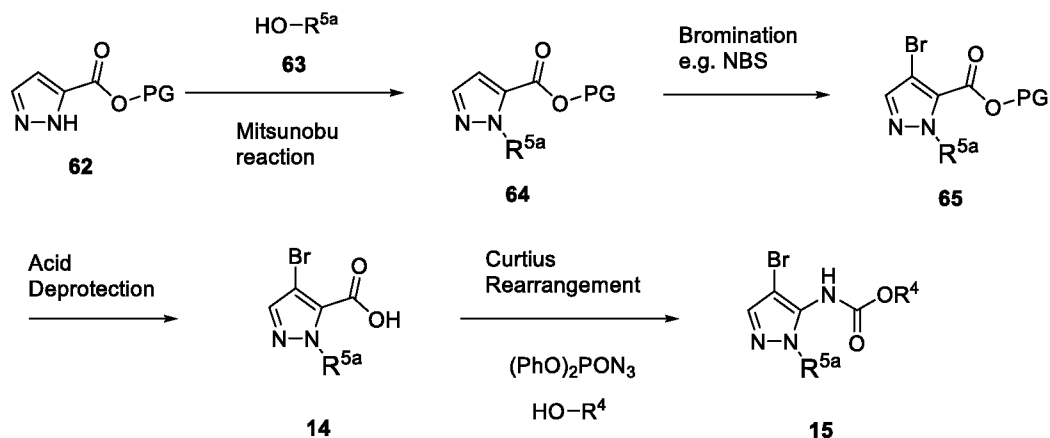
Scheme 10 describes the synthesis of the intermediate haloaryl oxabicyclo[2.2.2]ester **61**. The oxabicyclo[2.2.2] alcohol **51** is converted to the corresponding bromide (e.g. using a standard bromination protocol such as $\text{Ph}_3\text{P}/\text{CBr}_4$) **59**. Elimination of bromide **59** provides the vinyl oxabicyclo[2.2.2]octane intermediate **60**. Oxidative cleavage of the alkene **60** to the corresponding carboxylic acid, followed by acid protection, provides the desired haloaryl oxabicyclo[2.2.2]ester **61**.

Scheme 10



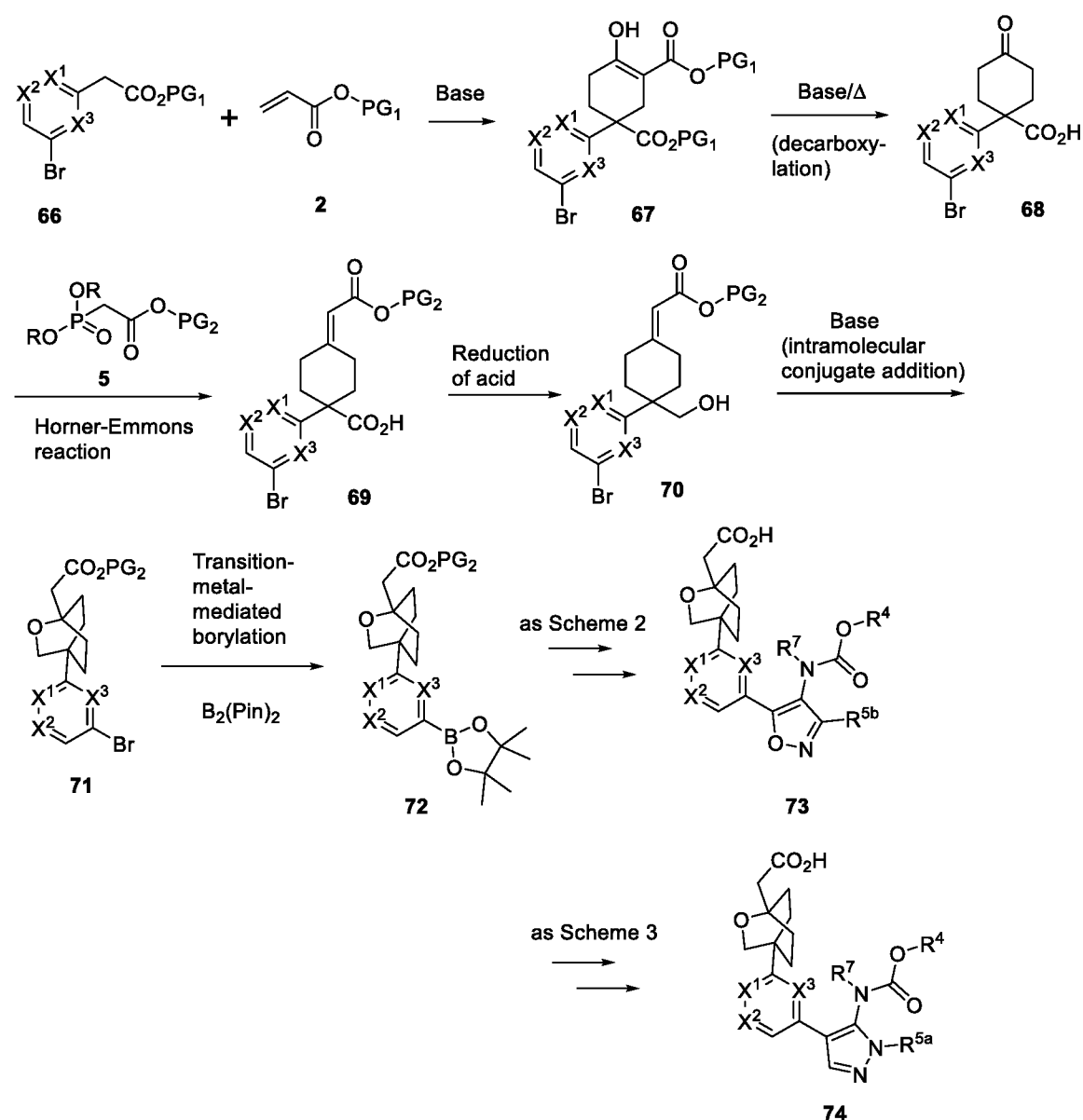
Scheme 11 describes the synthesis of 4-bromo-pyrazol-5-yl N-carbamates **15**. Pyrazole 5-carboxylate ester **62** is subjected to a Mitsunobu reaction (Kumara Swamy, K. C., *Chem. Rev.*, **2009**, *109*, 2551-2651) with alcohol **63** to give N-alkylated pyrazole ester **64**. Regioselective bromination (e.g. N-bromosuccinimide) of pyrazole ester **64** provides the 4-bromo-pyrazole ester **65**. Deprotection of the ester provides the bromo-pyrazole carboxylic acid **14**, which is subjected to a Curtius rearrangement in the presence of an alcohol **67** to provide the desired 4-bromo-pyrazol-5-yl N-carbamates **15**.

Scheme 11



- 5 Scheme 12 describes the synthesis of isoxazole 2-oxabicyclo[2.2.2]octan-1-yl aryl acetic acids **73** and pyrazole 2-oxabicyclo[2.2.2]octan-1-yl aryl acetic acids **74**. A double Michael reaction of the anion of a 3-bromophenyl acetic acid ester **66** with acrylate ester **2** (2 equivalents) provides the β -keto cyclohexyl ester **67**. Hydrolysis of diester **67** followed by decarboxylation of the intermediate β -keto-acid furnishes the cyclohexyl keto-acid **68**. Horner-Emmons reaction with phosphonate-ester **5** provides the α,β -unsaturated ester-acid **69**, which is reduced to the cyclohexyl alcohol **70**. The cyclohexyl α,β -unsaturated ester-alcohol **70** is subjected to a base-mediated intramolecular oxy-Michael reaction to provide the oxabicyclo[2.2.2] ester **71**. Reaction of the 3-haloarene **71** with bis(pinacolato)diboron in the presence of an appropriate transition metal catalyst (e.g. palladium, for instance Ishiyama, T. et al, *J. Org. Chem.* **1995**, *60*, 7508-7510) provides the corresponding pinacol boronate **72**, which is then converted to the desired oxabicyclo[2.2.2] isoxazole N-carbamate acids **73** using the procedures and general synthetic scheme described in Scheme 2. Similarly, the aryl pinacol boronate **72** is converted to the desired oxabicyclo[2.2.2] pyrazole N-carbamate acids **74** using the
- 10
- 15
- 20

Scheme 12



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.

5 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
10 standard. In the examples where ^1H NMR spectra were collected in d_6 -DMSO, a water-suppression sequence is often utilized. This sequence effectively suppresses the water signal and any proton peaks in the same region usually between 3.30-3.65 ppm which will affect the overall proton integration.

^1H NMR spectral data are typically reported as follows: chemical shift, multiplicity
15 (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.

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

20

HPLC-1: Sunfire C18 column (4.6×150 mm) $3.5 \mu\text{m}$, 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-2: XBridge Phenyl (4.6×150 mm) $3.5 \mu\text{m}$, 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)

30 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.

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

5 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.

10

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

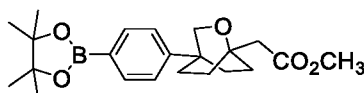
Mobile Phase A: 5:95 CH₃CN:water with 0.1% TFA;

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;

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

Intermediate 1. methyl 2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate



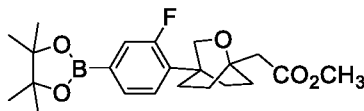
20 A solution of methyl 2-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate (340 mg, 1.00 mmol, prepared according to the procedures as described in US patent 8993619), KOAc (295 mg, 3.01 mmol) and bis(pinacolato)diboron (305 mg, 1.20 mmol) in DMSO (4 mL) was degassed by bubbling with Ar for 5 min, after which PdCl₂(dppf) (73.3 mg, 0.100 mmol) was added. The reaction mixture was heated to 85 °C for 5 h

25 under Ar, then was cooled to RT and partitioned between EtOAc (5 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (2 x 8 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound as

30 a white solid (310 mg, 0.80 mmol, 80% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d,

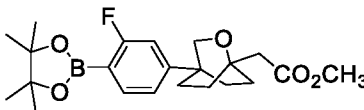
$J=8.4$ Hz, 2H), 7.31 (d, $J=8.4$ Hz, 2H), 4.04 (s, 2H), 3.72 (s, 3H), 2.50 (s, 2H), 2.19 - 1.81 (m, 8H), 1.42 - 1.30 (m, 12H).

Intermediate 2. methyl 2-(4-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxabicyclo [2.2.2]octan-1-yl)acetate



Intermediate 2 was prepared by the same synthetic sequence that was used to synthesize Intermediate 1. Methyl 2-(4-(4-bromo-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate was used as starting material instead of methyl 2-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate. ^1H NMR (400M Hz, CDCl_3) δ 7.51 (d, $J=7.7$ Hz, 1H), 7.42 (d, $J=13.0$ Hz, 1H), 7.12 (t, $J=7.7$ Hz, 1H), 4.14 (s, 2H), 3.69 (s, 3H), 2.47 (s, 2H), 2.22 - 1.99 (m, 6H), 1.96 - 1.85 (m, 2H), 1.32 (s, 12H).

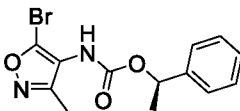
Intermediate 3. methyl 2-(4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate



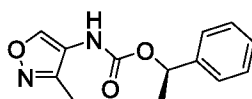
Intermediate 3 was prepared by the same synthetic sequence that was used to synthesize Intermediate 1. Methyl 2-(4-(4-bromo-3-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate was used as starting material instead of methyl 2-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate. ^1H NMR (400MHz, CDCl_3) δ 7.70 (dd, $J=7.8$, 6.7 Hz, 1H), 7.07 (dd, $J=7.8$, 1.7 Hz, 1H), 6.95 (dd, $J=11.2$, 1.5 Hz, 1H), 4.01 (s, 2H), 3.72 (s, 3H), 2.50 (s, 2H), 2.22 - 2.03 (m, 4H), 2.00 - 1.85 (m, 4H), 1.37 (s, 10H).

25

Intermediate 4. (R)-1-phenylethyl (5-bromo-3-methylisoxazol-4-yl)carbamate



Intermediate 4A. (R)-1-phenylethyl (3-methylisoxazol-4-yl)carbamate

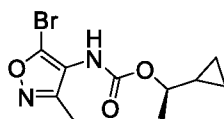


A mixture of 3-methylisoxazole-4-carboxylic acid (2.0 g, 15.7 mmol), (PhO)₂PON₃ (4.24 mL, 18.9 mmol), (R)-1-phenylethanol (2.11 g, 17.3 mmol), Et₃N (2.85 mL, 20.5 mmol) in toluene (40 mL) was stirred at 80 °C for 4 h, then was cooled to RT and concentrated *in vacuo*. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 25 min) to give the title compound as white solid (2.31g, 9.38 mmol, 59.6% yield). LCMS [M + H]⁺ = 247.0; ¹H NMR (400 MHz, CDCl₃) δ 8.66 (br. S., 1H), 7.38 (d, *J*=4.4 Hz, 5H), 6.08 (br. S., 1H), 5.89 (q, *J*=6.6 Hz, 1H), 2.26 (s, 3H), 1.62 (d, *J*=6.6 Hz, 3H).

Intermediate 4

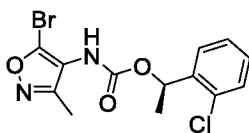
To a solution of intermediate 4A (248 mg, 1.01 mmol) in CH₃CN (10 mL) was slowly added NBS (233 mg, 1.31 mmol). The reaction mixture was stirred at RT overnight, then was concentrated *in vacuo*. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound as a light yellow solid (241 mg, 0.73mmol, 72.9% yield). LCMS [M + H]⁺ = 327.0; ¹H NMR (400 MHz, CDCl₃) δ 7.44 - 7.28 (m, 5H), 5.94 - 5.83 (m, 1H), 5.82 - 5.68 (m, 1H), 2.23 (s, 3H), 1.60 (d, *J*=6.8 Hz, 3H).

Intermediate 5. (R)-1-cyclopropylethyl (5-bromo-3-methylisoxazol-4-yl)carbamate



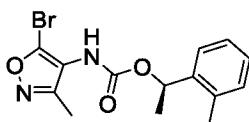
Intermediate 5 was prepared by the same synthetic sequence that was used to synthesize Intermediate 4 from 3-methyl isoxazole-4-carboxylic acid, except that (R)-1-cyclopropylethanol was used as starting material instead of (R)-1-phenylethanol. ¹H NMR (400 MHz, CDCl₃) δ 5.83 (br. s., 1H), 4.31 (dq, *J*=8.8, 6.3 Hz, 1H), 2.32 (s, 3H), 1.38 (d, *J*=5.1 Hz, 3H), 1.02 (br. s., 1H), 0.77 - 0.17 (m, 4H).

Intermediate 6. (R)-1-(2-chlorophenyl)ethyl (5-bromo-3-methylisoxazol-4-yl)carbamate



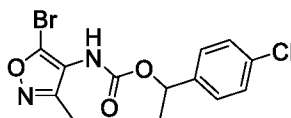
Intermediate 6 was prepared by the same synthetic sequence that was used to synthesize Intermediate 4 from 3-methyl isoxazole-4-carboxylic acid, except that (R)-1-(2-chlorophenyl) ethanol was used as starting material instead of (R)-1-phenylethanol. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J*=8.1 Hz, 3H), 7.25 (br. s., 1H), 6.22 (q, *J*=6.6 Hz, 1H), 5.91 (br. s., 1H), 2.26 (s, 3H), 1.66 - 1.58 (m, 3H).

Intermediate 7. (R)-1-(o-tolyl)ethyl (5-bromo-3-methylisoxazol-4-yl)carbamate



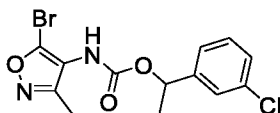
Intermediate 7 was prepared by the same synthetic sequence that was used to synthesize Intermediate 4 from 3-methyl isoxazole-4-carboxylic acid, except that (R)-1-(o-tolyl)ethan-1-ol was used as starting material instead of (R)-1-phenylethanol. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (br. s., 1H), 7.27 - 7.15 (m, 3H), 6.09 (q, *J*=6.6 Hz, 1H), 5.92 (br. s., 1H), 2.41 (s, 3H), 2.26 (s, 3H), 1.61 (d, 3H).

Intermediate 8. (±)-1-(4-chlorophenyl)ethyl (5-bromo-3-methylisoxazol-4-yl)carbamate



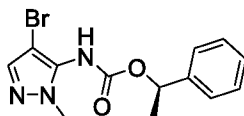
Intermediate 8 was prepared by the same synthetic sequence that was used to synthesize Intermediate 4 from 3-methyl isoxazole-4-carboxylic acid, except that (±)-1-(4-chlorophenyl) ethan-1-ol was used as starting material instead of (R)-1-phenylethanol. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J*=6.2 Hz, 4H), 5.96 - 5.87 (m, 1H), 5.83 (q, *J*=6.6 Hz, 1H), 2.24 (s, 3H), 1.59 (d, *J*=1.0 Hz, 3H).

Intermediate 9. (±)-1-(3-chlorophenyl)ethyl (5-bromo-3-methylisoxazol-4-yl)carbamate



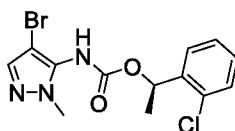
Intermediate 9 was prepared by the same synthetic sequence that was used to synthesize Intermediate 4 from 3-methyl isoxazole-4-carboxylic acid, except that (±)-1-(3-chlorophenyl) ethan-1-ol was used as starting material instead of (R)-1-phenylethanol. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (s, 1H), 7.31 (br. s., 3H), 6.35 - 6.14 (m, 1H), 5.85 (q, *J*=6.6 Hz, 1H), 3.77 (s, 3H), 1.62 (bs, 3H; overlapping with water peak).

Intermediate 10. (R)-1-phenylethyl (4-bromo-1-methyl-1H-pyrazol-5-yl)carbamate



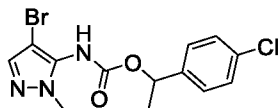
A mixture of 4-bromo-1-methyl-1H-pyrazole-5-carboxylic acid (200 mg, 0.97 mmol), (PhO)₂PON₃ (254 μL, 1.17 mmol) and (R)-1-phenylethanol (125 mg, 1.02 mmol), TEA (272 μL, 1.95 mmol) in toluene (3 mL) was stirred at 80 °C for 1 h, then was cooled to RT and concentrated *in vacuo*. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound (200 mg, 0.617 mmol, 63.2 % yield). LCMS [M + H]⁺ = 325.8; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J*=8.4 Hz, 2H), 7.37 (d, *J*=8.8 Hz, 2H), 5.94 (br. s., 1H), 4.02 (s, 2H), 4.01 - 3.95 (m, 2H), 3.70 (s, 3H), 2.49 (s, 2H), 2.29 (s, 3H), 2.11 (d, *J*=9.2 Hz, 4H), 2.01 - 1.85 (m, 4H), 0.93 - 0.74 (m, 1H), 0.67 - 0.21 (m, 4H).

Intermediate 11. (R)-1-(2-chlorophenyl)ethyl (4-bromo-1-methyl-1H-pyrazol-5-yl)carbamate



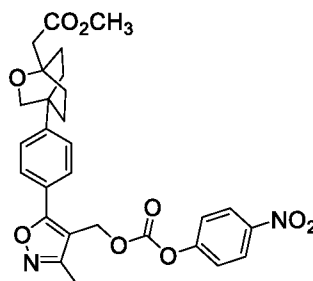
Intermediate 11 was prepared by the same procedure that was used to synthesize Intermediate 10, by using (R)-1-(2-chlorophenyl)ethanol as starting material instead of (R)-1-phenylethanol. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1H), 7.41 - 7.27 (m, 3H), 7.24 (s, 1H), 6.22 (q, *J*=6.5 Hz, 1H), 6.16 - 6.04 (m, 1H), 3.76 (s, 3H), 1.59 (d, *J*=5.3 Hz, 3H).

Intermediate 12. (±)-1-(4-chlorophenyl)ethyl (4-bromo-1-methyl-1H-pyrazol-5-yl)carbamate

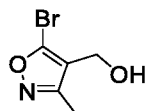


Intermediate 12 was prepared by the same procedure that was used to synthesize Intermediate 10, by using (±)-1-(4-chlorophenyl)ethan-1-ol as starting material instead of (R)-1-phenylethanol. ¹H NMR (400 MHz, CDCl₃) δ: 7.47 (s, 1H), 7.30-7.42 (m, 4H), 6.01-6.36 (m, 1H), 5.86 (q, J=6.6 Hz, 1H), 3.76 (s, 3H), 1.61 (s, 3H).

Intermediate 13. methyl 2-(4-(4-(3-methyl-4-(((4-nitrophenoxy)carbonyl)oxy)methyl)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate

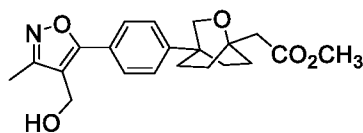


Intermediate 13A. (5-bromo-3-methylisoxazol-4-yl)methanol



To a solution of ethyl 5-bromo-3-methylisoxazole-4-carboxylate (480 mg, 2.05 mmol) in THF added DIBALH (6.5 mL of a 1M solution in DCM; 6.50 mmol) dropwise over 5 min at RT. The reaction was stirred at RT for 1 h, then was quenched with aq. sodium potassium tartrate (10 mL of a 1 M solution) & stirred at RT for 1 h. The resultant mixture was filtered through a plug of Celite[®]; the plug was washed with EtOAc (2 x 5 mL) and concentrated *in vacuo* to give the title compound as a white solid (334 mg, 1.74 mmol, 85% yield). LCMS [M + H]⁺=193.9; ¹H NMR (CDCl₃) δ: 4.51 (s, 2H), 2.40 (s, 3H).

Intermediate 13B. methyl 2-(4-(4-(4-(hydroxymethyl)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate

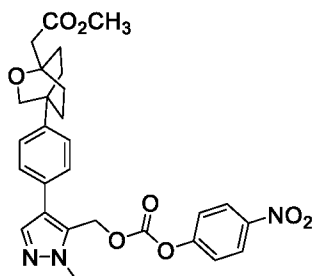


To a solution of Intermediate 1 (40.2 mg, 0.10 mmol) and Intermediate 13A (20 mg, 0.104 mmol) in THF/water was added K_2CO_3 (43.2 mg, 0.31 mmol). The solution was degassed under N_2 , after which $PdCl_2(dppf)$ (7.6 mg, 10.4 μ mol) was added. The reaction mixture was heated in a sealed tube at 80°C for 18 h, then was cooled to RT and filtered through a plug of Celite. The Celite plug was washed with EtOAc (2 X 2 mL). The combined filtrates were partitioned between water and EtOAc (5 mL each). The aqueous layer was extracted with EtOAc (3 X 2 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2 ; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound as a light yellow oil (18 mg, 0.068 mmol, 46.5% yield). LCMS $[M + H]^+ = 373.1$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, $J=8.6$ Hz, 2H), 7.42 (d, $J=8.6$ Hz, 2H), 4.66 (s, 2H), 4.06 (s, 2H), 3.73 (s, 3H), 2.51 (s, 2H), 2.40 (s, 3H), 2.14 (d, $J=8.6$ Hz, 4H), 1.95 (d, $J=7.5$ Hz, 4H).

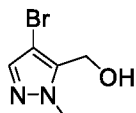
Intermediate 13

To a solution of Intermediate 13B (18 mg, 0.048 mmol) in DCE (1 mL) was added pyridine (0.020 mL, 0.24 mmol), followed by 4-nitrophenyl chloroformate (19.5 mg, 0.097 mmol). The reaction mixture was stirred at RT for 18 h, then was filtered and concentrated *in vacuo*. The residue was chromatographed (SiO_2 ; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound as a light yellow solid (16 mg, 0.030 mmol, 60.5% yield). LCMS $[M + H]^+ = 537.2$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, $J=9.2$ Hz, 2H), 7.77 (d, $J=8.6$ Hz, 2H), 7.44 (dd, $J=18.0, 9.0$ Hz, 4H), 5.29 (s, 2H), 4.07 (s, 2H), 3.73 (s, 3H), 2.52 (s, 2H), 2.46 (s, 3H), 2.15 (d, $J=8.6$ Hz, 4H), 2.05 - 1.87 (m, 4H).

Intermediate 14. methyl 2-(4-(4-(1-methyl-5-((((4-nitrophenoxy)carbonyl)oxy)methyl)-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate

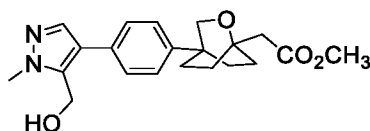


Intermediate 14A. (4-bromo-1-methyl-1H-pyrazol-5-yl)methanol



5 To a solution of ethyl 5-bromo-3-methylisoxazole-4-carboxylate (480 mg, 2.05 mmol)) in THF added DIBALH (6.5 mL of a 1M solution in DCM; 6.50 mmol) dropwise over 5 min at RT. The reaction was stirred at RT for 1 h, then was quenched with aq. sodium potassium tartrate (10 mL of a 1 M solution) & stirred at RT for 1 h. The resultant mixture was filtered through a plug of Celite; the plug was washed with EtOAc (2 x 5
10 mL) and concentrated *in vacuo* to give the title compound as a white solid (334 mg, 1.74 mmol, 85% yield). LCMS $[M + H]^+ = 193.9$; ^1H NMR ($CDCl_3$) δ : 4.51 (s, 2H), 2.40 (s, 3H).

Intermediate 14B. methyl 2-(4-(4-(5-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-
15 2-oxabicyclo[2.2.2] octan-1-yl)acetate



To a solution of Intermediate 1 (101 mg, 0.26 mmol) and Intermediate 14A (50 mg, 0.26 mmol) in THF/water was added K_2CO_3 (109 mg, 0.79 mmol). The solution was degassed under N_2 , after which $PdCl_2(dppf)$ (19.2 mg, 0.026 mmol) was added. The
20 reaction was heated in a sealed tube at 80 °C for 18 h, then was cooled to RT and filtered through a plug of Celite. The Celite plug was washed with EtOAc (2 X 2 mL). The combined filtrates were partitioned between water and EtOAc (5 mL each). The aqueous layer was extracted with EtOAc (3 X 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed
25 (SiO_2 ISCO column; continuous gradient from 0% to 100% EtOAc in hexanes over 20

min) to give the title compound as a light yellow oil (75 mg, 0.20 mmol, 77% yield).

LCMS $[M + H]^+ = 372.1$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.32 - 7.15 (m, 5H), 4.67 (d, $J=5.1$ Hz, 2H), 3.99 - 3.87 (m, 5H), 3.63 (s, 3H), 2.41 (s, 2H), 2.04 (d, $J=7.0$ Hz, 4H), 1.91 - 1.80 (m, 4H).

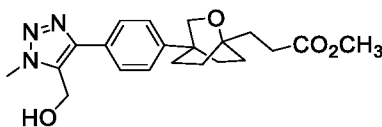
5

Intermediate 14

To a solution of Intermediate 14B (75 mg, 0.20 mmol) in DCE (2 mL) were successively added pyridine (0.082 mL, 1.01 mmol) and 4-nitrophenyl chloroformate (73.5 mg, 0.36 mmol). The reaction mixture was stirred at RT for 18 h, then was filtered and concentrated *in vacuo*. The residue was chromatographed (SiO_2 ISCO column; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound as a light yellow solid (76 mg, 0.14 mmol, 70% yield). LCMS $[M + H]^+ = 536.1$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, $J=9.2$ Hz, 1H), 7.64 (s, 1H), 7.47 - 7.33 (m, 7H), 5.41 (s, 2H), 4.06 (s, 5H), 3.73 (s, 3H), 2.52 (s, 2H), 2.15 (d, $J=7.0$ Hz, 4H), 2.04 - 1.89 (m, 4H).

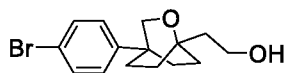
15

Intermediate 15. methyl 3-(4-(4-(5-(hydroxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)propanoate



20

Intermediate 15A. 2-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)ethan-1-ol



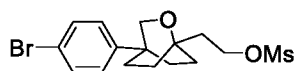
To a 0°C solution of methyl 2-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate (1.01g, 2.98 mmol, prepared according to the procedures described in US patent 8993619) in THF (59.5 mL) was added DIBALH (14.9 mL of a 1 M solution in THF, 14.9 mmol). After stirring at 30 min at 0°C, the reaction was quenched with aq. sodium potassium tartrate (60 mL). The aqueous layer was extracted with EtOAc (3 X 60 mL); the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.97 g, 3.12 mmol, 105 % yield) as an oil. ^1H NMR (400 MHz,

25

CDCl₃) 7.44 (d, J=8.6 Hz, 2H), 7.14 (d, J=8.6 Hz, 2H), 3.96 (s, 2H), 3.81 (br. s., 2H), 3.32 - 3.07 (m, 1H), 2.21 - 1.84 (m, 6H), 1.82 - 1.63 (m, 4H).

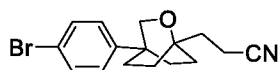
Intermediate 15 B. 2-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)ethyl

5 methanesulfonate



To a 0°C solution of Intermediate 15A (1.0 g, 3.21 mmol) in THF (32.1 mL) was added Et₃N (2.24 mL, 16.1 mmol) and methanesulfonyl chloride (0.376 mL, 4.82 mmol) at 0 °C and the reaction was stirred at RT for 30 min. LCMS showed that the reaction was complete. Satd aq. NaHCO₃ (10 mL) was added slowly to the reaction mixture. The mixture was extracted with EtOAc (2 x 20 mL), and the combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give Intermediate 15B (1.3 g, 3.34 mmol, 104 % yield) as an oil, which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J=8.8 Hz, 2H), 7.13 (d, J=8.6 Hz, 2H), 4.38 (t, J=7.0 Hz, 2H), 3.94 (s, 2H), 3.01 (s, 3H), 2.10 - 1.84 (m, 8H), 1.80 - 1.64 (m, 2H).

Intermediate 15 C. 3-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)propanenitrile



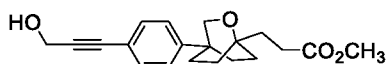
To a solution of Intermediate 15B (1.3 g, 3.34 mmol) in DMSO (33.4 mL) were added NaCN (0.491 g, 10.02 mmol) and Bu₄NI (0.123 g, 0.334 mmol) and the reaction was stirred at 90 °C for 16 h, after which LCMS showed presence of desired product. The reaction was cooled to RT and H₂O (10 mL) was added slowly to the reaction mixture. The mixture was then extracted with EtOAc (2 x 20 mL), and the combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound (0.85 g, 2.65 mmol, 79 % yield). ¹H NMR (400 MHz, CDCl₃) δ 7.53 - 7.40 (m, 2H), 7.20 - 7.08 (m, 2H), 3.99 - 3.89 (m, 2H), 2.55 - 2.37 (m, 2H), 2.16 - 1.90 (m, 6H), 1.87 - 1.65 (m, 4H).

30 Intermediate 15 D. methyl 3-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)propanoate



Preparation of a 3.6 M HCl solution in MeOH/MeOAc: To a solution of MeOH (30 mL) at 0 °C was added dropwise acetyl chloride (10 mL, d = 1.104 g/mL, MW = 78.49). Upon completion of the addition, the resulting solution was warmed to RT for 30 min. This 3.6 M HCl solution in MeOH/MeOAc (36.9 mL, 133 mmol) was added to Intermediate 15C (850 mg, 2.65 mmol) and the reaction was stirred at RT for 72 h. The reaction mixture was diluted with MeCN (25 mL) and was concentrated in vacuo to remove MeOH and MeCN. The residue was dissolved in EtOAc (30 mL) and washed with satd aq NaHCO₃ (2 X 30 mL), water (30 mL), and brine (30 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound (810 mg, 2.293 mmol, 86 % yield) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J*=8.6 Hz, 2H), 7.21 - 6.99 (m, 2H), 4.00 - 3.84 (m, 2H), 3.67 (s, 3H), 2.49 - 2.28 (m, 2H), 2.12 - 1.85 (m, 6H), 1.82 - 1.73 (m, 2H), 1.71 - 1.60 (m, 2H), 1.35 - 1.18 (m, 1H), 0.92 - 0.75 (m, 1H).

Intermediate 15 E. methyl 3-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)propanoate

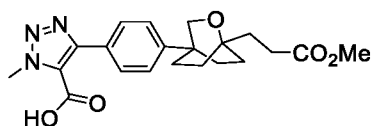


To a degassed solution of Intermediate 15D (200 mg, 0.566 mmol) in THF (2.8 ml) were added successively: CuI (10.8 mg, 0.057 mmol), Pd(PPh₃)₄ (65.4 mg, 0.057 mmol), and DBU (0.25 mL, 1.70 mmol). The resulting mixture was degassed again and prop-2-yn-1-ol (0.1 mL, 1.70 mmol) was added over 10 min. The reaction mixture was slowly heated to 60°C and then stirred at 60°C overnight, then was cooled to RT and diluted with ether (50 mL). The mixture was washed with water (20 mL), 15 % aq. HCl (2 x 20 mL) and satd aq. NaHCO₃ (25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound (160 mg, 86%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.46 - 7.35 (m, 2H), 7.25 - 7.11 (m, 2H), 4.57 - 4.46 (m, 2H), 4.03 - 3.91 (m, 2H), 3.77 - 3.61 (m, 2H), 2.49 - 2.35 (m, 4H), 2.04 - 1.85 (m, 4H), 1.84 - 1.75 (m, 2H), 1.72 - 1.66 (m, 2H).

Intermediate 15

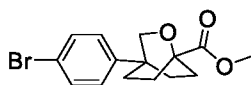
A solution of Intermediate 15E (160 mg, 0.487 mmol) in toluene (0.5 ml) and TMSCH₂N₃ (315 mg, 2.44 mmol) was heated at reflux under Ar for 15 h, then was cooled to RT. Volatiles were removed in vacuo and the residue was dissolved in THF (0.5 mL). To the mixture was added Bu₄NF (0.5 mL of a 1 M solution in THF, 0.50 mmol) at 0 °C. After stirring for 10 min at 0 °C, the reaction mixture was concentrated in vacuo and the residue was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound (35 mg, 19%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.65 - 7.55 (m, 2H), 7.35 - 7.30 (m, 2H), 4.87 - 4.81 (m, 2H), 4.11 - 4.08 (m, 3H), 3.98 - 3.95 (m, 2H), 3.71 - 3.67 (m, 3H), 2.45 - 2.38 (m, 2H), 2.13 - 2.06 (m, 2H), 2.00 - 1.89 (m, 4H), 1.84 - 1.76 (m, 2H), 1.73 - 1.61 (m, 2H).

Intermediate 16. 4-(4-(1-(3-methoxy-3-oxopropyl)-2-oxabicyclo[2.2.2]octan-4-yl)phenyl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid

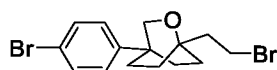


To a 0°C solution of Intermediate 15 (16 mg, 0.043 mmol) in acetone (1.4 mL) was added Jones reagent (0.3 mL, 0.90 mmol). The reaction mixture was stirred at 0 °C for 1 h, after which iPrOH (1 mL) was added and volatiles were concentrated in vacuo. Water (10 mL) was added and the mixture was extracted with EtOAc (3 X 10 mL). The combined organic extracts were concentrated in vacuo to give the title compound (16 mg, 0.042 mmol, 96 % yield). This material was used for the next step without further purification. LCMS [M + H]⁺ = 386.1.

Intermediate 17. methyl 4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octane-1-carboxylate

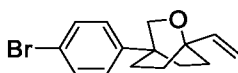


Intermediate 17A. 1-(2-bromoethyl)-4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octane



To a 0 °C solution of 2-(4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)ethanol (2.5 g, 8.03 mmol) in DCM (2 mL) were successively added CBr₄ (4.00 g, 12.1 mmol) and Ph₃P (2.53 g, 9.64 mmol). The reaction mixture was stirred at 0 °C for 2 h, then was allowed to warm to RT and stirred at RT for 2 h, after which it was concentrated in vacuo. The residue was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound (2.8 g, 93%). ¹H NMR (400 MHz, CDCl₃) 7.53 - 7.43 (m, 2H), 7.22 - 7.10 (m, 2H), 4.10 - 3.85 (m, 2H), 3.57 - 3.36 (m, 2H), 2.16 - 1.86 (m, 8H), 1.79 - 1.62 (m, 2H).

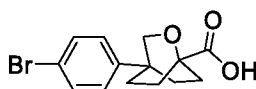
10 Intermediate 17B. 4-(4-bromophenyl)-1-vinyl-2-oxabicyclo[2.2.2]octane



To a solution of Intermediate 17A (2.70 g, 7.22 mmol) in DMSO (144 mL) was added KOtBu (1.22 g, 10.83 mmol). The reaction mixture was stirred at 80 °C for 1 h, then was cooled to RT, after which sat'd aq. NaHCO₃ (10 mL) was slowly added. The mixture was extracted with EtOAc (2 x 20 mL) and the combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo to give the title compound (1.70 g, 80%). ¹H NMR (400 MHz, CDCl₃) 7.58 - 7.40 (m, 2H), 7.22 - 7.11 (m, 2H), 5.98 - 5.83 (m, 1H), 5.27 - 5.17 (m, 1H), 5.12 - 4.98 (m, 1H), 4.14 - 3.99 (m, 2H), 2.19 - 2.02 (m, 4H), 2.00 - 1.93 (m, 2H), 1.89 - 1.79 (m, 2H).

20

Intermediate 17C. 4-(4-bromophenyl)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid



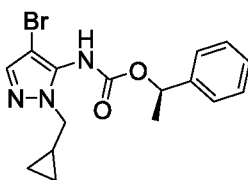
To a solution of Intermediate 17B (600 mg, 2.05 mmol) in MeCN (3 mL), CCl₄ (3 mL) and water (3 mL) was added NaIO₄ (1.7 g, 8.19 mmol) and Ru(III)Cl₃ (42.4 mg, 0.205 mmol). The reaction mixture was stirred at RT for 23 h, then was filtered. The filtrate was diluted with EtOAc (10 mL) and washed with 1N aq. HCl (10 mL), then was concentrated in vacuo. The crude material was triturated with EtOAc (3 mL) to give the title compound (600 mg, 1.928 mmol, 94 % yield) as a solid. ¹H NMR (400 MHz, CDCl₃) 7.42 - 7.34 (m, 2H), 7.11 - 6.99 (m, 2H), 4.10 - 3.98 (m, 2H), 2.24 - 1.76 (m, 8H).

30

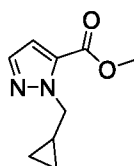
Intermediate 17

To a 0 °C solution of Intermediate 17C (300 mg, 0.964 mmol) in THF (0.3 mL)/MeOH (0.6 mL) was added TMSCHN₂ (0.482 mL of a 2 M solution in Et₂O, 0.964 mmol) dropwise. The reaction mixture was slowly warmed to RT and stirred at RT for 1 h. Volatiles were removed in vacuo. The crude product was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound (300 mg, 96%). ¹H NMR (400 MHz, CDCl₃) 7.34 - 7.25 (m, 2H), 7.01 - 6.89 (m, 2H), 3.93 - 3.86 (m, 2H), 3.84 - 3.70 (m, 3H), 2.03 - 1.33 (m, 8H).

Intermediate 18. (R)-1-phenylethyl (4-bromo-1-(cyclopropylmethyl)-1H-pyrazol-5-yl)carbamate

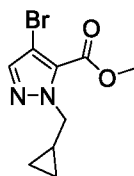


18A. methyl 1-(cyclopropylmethyl)-1H-pyrazole-5-carboxylate



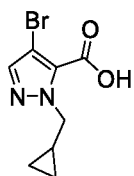
To a solution of methyl 1H-pyrazole-5-carboxylate (100 mg, 0.793 mmol), cyclopropyl-methanol (68 mg, 0.952 mmol), and Ph₃P (260 mg, 0.991 mmol) in DCM (1 mL) was added DEAD (176 μL, 1.11 mmol) at RT. The reaction mixture was stirred at RT for 16 h, then was concentrated in vacuo. The crude material was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to afford the title compound (45 mg, 0.25 mmol, 31.5 % yield) as a clear, colorless oil. ¹H NMR (400 MHz, CDCl₃) 7.27 (d, *J*=2.0 Hz, 1H), 6.62 (d, *J*=2.0 Hz, 1H), 4.22 (d, *J*=7.3 Hz, 2H), 3.66 (s, 3H), 1.21 - 0.99 (m, 1H), 0.30 (s, 2H), 0.22 - 0.10 (m, 2H).

18B. methyl 4-bromo-1-(cyclopropylmethyl)-1H-pyrazole-5-carboxylate



A mixture of Intermediate 18A (45 mg, 0.250 mmol) and NBS (49 mg, 0.275 mmol) in MeCN (1.25 mL) was stirred at RT for 16 h, then was concentrated in vacuo. The crude product was chromatographed (24 g SiO₂; continuous gradient from 0-50% EtOAc in hexanes over 15 min) to afford crude Intermediate 18B (30 mg, 0.116 mmol, 46.4 % yield) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.37 - 7.17 (m, 1H), 4.38 - 4.07 (m, 2H), 3.80 - 3.63 (m, 3H), 0.69 - 0.64 (m, 1H), 0.39 - 0.28 (m, 2H), 0.21 - 0.11 (m, 2H).

10 Intermediate 18C. 4-bromo-1-(cyclopropylmethyl)-1H-pyrazole-5-carboxylic acid



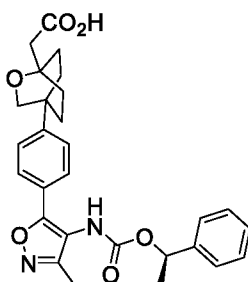
To a stirred solution of crude Intermediate 18B (40 mg, 0.154 mmol) in THF (1.5 mL), MeOH (0.100 mL) and water (0.15 mL) at RT was added 2.0 M aq. LiOH (0.23 mL, 0.463 mmol). The reaction mixture was stirred at RT for 16 h, then was acidified by dropwise addition of 1M aq. HCl (0.5 mL). The aqueous layer was extracted with EtOAc (3 X 3 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give the title compound (40 mg, 0.163 mmol, 106 % yield). LCMS [M + H]⁺ = 246.9.

20 Intermediate 18

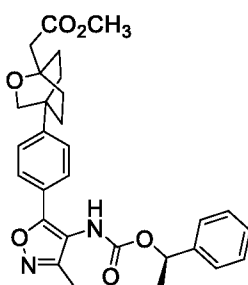
A mixture of Intermediate 18C (35 mg, 0.143 mmol), (PhO)₂PON₃ (0.040 mL, 0.186 mmol), (R)-1-phenylethanol (0.023 mL, 0.186 mmol), and TEA (0.10 mL, 0.714 mmol) in toluene (5 mL) was stirred at 80 °C for 1 h, then was cooled to RT and concentrated in vacuo. The crude oil was chromatographed (4 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (36 mg, 0.099 mmol, 69.2 % yield) as a clear oil. ¹H NMR (400 MHz, CDCl₃) 7.14 - 6.82 (m, 5H), 6.14

- 5.81 (m, 1H), 5.73 - 5.56 (m, 1H), 3.74 - 3.53 (m, 2H), 1.47 - 1.24 (m, 4H), 1.03 - 0.83 (m, 1H), 0.33 - 0.22 (m, 2H), 0.10 - -0.01 (m, 2H).

Example 1. 2-(4-(4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo [2.2.2]octan-1-yl)acetic acid



1A. methyl 2-(4-(4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate



10

A solution of Intermediate 1 (50 mg, 0.13 mmol), Intermediate 4 (42 mg, 0.13 mmol), K₂CO₃ (54 mg, 0.39 mmol) and PdCl₂(dppf) (10 mg, 0.013 mmol) in THF (5 mL) and water (1.25 mL) was purged with Ar for 5 min. The reaction mixture was then heated to 80 °C for 18 h under Ar, then was cooled to RT and filtered through Celite. The filterate was partitioned between EtOAc (3 mL) and water (3 mL); the aqueous phase was extracted with EtOAc (2x3 mL). The combined organic extracts were washed with water (2 mL), brine (2 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was chromatographed (SiO₂ ISCO column; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give title compound as a colorless oil. (23 mg, 0.045 mmol, 34.5% yield) LCMS [M + H]⁺ = 505.0; ¹H NMR (400 MHz, CDCl₃) δ 8.00 - 7.23 (m, 9H), 5.87 (d, *J*=6.4 Hz, 2H), 4.01 (s, 2H), 3.70 (s, 3H), 2.49 (s, 3H), 2.21 (s, 3H), 2.16 - 2.04 (m, 4H), 2.00 - 1.88 (m, 4H), 1.70 - 1.59 (m, 2H).

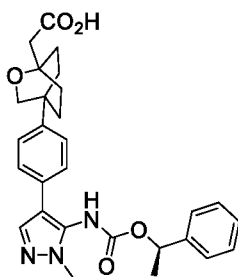
20

Example 1

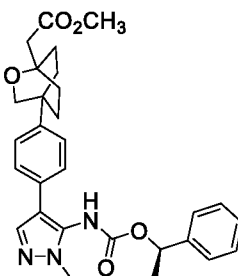
To a solution of compound 1A (22 mg, 0.044 mmol) in THF (1 mL) was added 1M aq. LiOH (0.44 mL, 0.44 mmol). The reaction was stirred at RT for 18 h, then was concentrated *in vacuo*. The residue was dissolved in H₂O (1 mL), and the pH was
 5 adjusted with 1N aq. HCl to ~3 and extracted with EtOAc (2 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by preparative LC/MS: Column: Waters XBridge C18, 19 x 200 mm, 5-μm particles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5-μm particles; Mobile Phase A: 5:95 MeCN:H₂O with 0.1% TFA; Mobile Phase B: 95:5
 10 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 concentrated *in vacuo* by centrifugal evaporation to give the title compound (11 mg, 0.023mmol, 52.3% yield). LCMS [M + H]⁺=491.2; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (br. s., 2H), 7.22 (d, J=6.6 Hz, 6H), 7.10 - 6.90 (m, 1H), 6.01 - 5.72 (m, 2H), 4.03 (s, 2H),
 15 2.49 (s, 2H), 2.14 (s, 3H), 2.09 - 1.72 (m, 8H), 1.55 (br. s., 3H); hLPA₁ Antagonist IC₅₀ = 116 nM.

Example 2. 2-(4-(4-(1-methyl-5-(((R)-1-phenylethoxy)carbonyl)amino)-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid

20



2A. methyl 2-(4-(4-(1-methyl-5-(((R)-1-phenylethoxy)carbonyl)amino)-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate

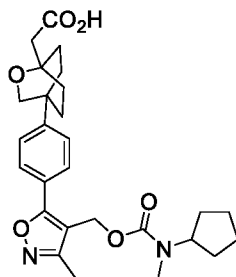


A solution of Intermediate 1 (20 mg, 0.052 mmol), Pd(OAc)₂ (2.3 mg, 10.4 μmol), K₃PO₄ (33 mg, 0.16 mmol) and Xphos (5 mg, 10.4 μmol) in toluene (1.5 mL) and water (0.2 mL) was purged with Ar for 5 min, then was heated to 100 °C for 4 h under Ar. After cooling to RT, the reaction mixture was filtered through Celite. The filtrate was partitioned between EtOAc (2 mL) and water (2 mL); the aqueous phase was extracted with EtOAc (2x1 mL). The combined organic extracts were washed with water (1 mL), brine (1 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was chromatographed (SiO₂ ISCO column; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound. (13 mg, 0.026 mmol, 49.9 % yield). LCMS [M + H]⁺ = 504.0; ¹H NMR (400 MHz, CDCl₃) δ: 7.55-7.73 (m, 1H), 7.28-7.47 (m, 6H), 7.17-7.23 (m, 2H), 6.07-6.20 (m, 1H), 5.89 (br d, 1H), 4.01 (s, 2H), 3.65-3.85 (m, 6H), 2.49 (s, 2H), 2.10 (br d, 3H), 1.86-1.96 (m, 3H), 1.60 (br d, 3H), 1.20-1.37 (m, 3H).

Example 2

To a stirred solution of compound 2A (13 mg, 0.026 mmol) in THF (1.0 mL) and water (0.5 mL) at RT was added 2.0 M aq LiOH (0.039 mL, 0.077 mmol). The reaction mixture was stirred at RT for 5 h, then was concentrated *in vacuo*. The residue was dissolved in H₂O (1 mL), and the pH was adjusted with 1N aq. HCl to ~3 and extracted with EtOAc (2 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by preparative LC/MS: Column: Waters XBridge C18, 19 x 200 mm, 5-μm particles; Guard Column: Waters XBridge C18, 19 x 10 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: 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 concentrated *in vacuo* by centrifugal evaporation to give the title compound (8 mg, 0.016 mmol, 60.8 % yield). LCMS [M + H]⁺ = 490.1; ¹H NMR (400 MHz, CD₃CN) δ 7.55 (s, 1H), 7.43 - 6.93 (m, 9H), 5.74 - 5.45 (m, 1H), 3.92 (s, 2H), 3.58 (s, 3H), 2.35 (s, 2H), 2.10 - 1.64 (m, 8H), 1.54 - 1.20 (m, 3H); hLPA₁ IC₅₀ = 88 nM.

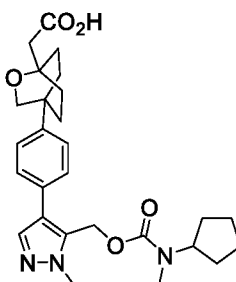
Example 3. 2-(4-(4-(4-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid



To a solution of Intermediate 13 (3.5 mg, 6.52 μ mol) in THF (1 mL) was added
 5 iPr_2NEt (2.3 μ L, 0.013 mmol) followed by N-methylcyclopentanamine (0.65 mg, 6.5 μ mol). The reaction mixture was stirred at RT for 18 h, after which 2M aq. LiOH (33 μ L, 0.065 mmol) was added. The reaction was stirred at RT for 18 h, then was concentrated *in vacuo*. The residue was dissolved in H₂O (1 mL), and the pH was adjusted with 1N aq. HCl to ~3 and extracted with EtOAc (2 x 1 mL). The combined organic extracts were
 10 washed with brine (1 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by 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.
 15 Fractions containing the desired product were combined and concentrated *in vacuo* by centrifugal evaporation to give the title compound (2.7 mg, 5.6 μ mol, 86% yield). LCMS $[M + H]^+ = 483.4$; ¹H NMR (400 MHz; DMSO-d₆) δ : 7.75 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.2 Hz, 2H), 5.07 (s, 2H), 3.93 (s, 2H), 3.41 (s, 1H), 2.67 (s, 3H), 2.30-2.37 (m, 5H), 1.82-2.08 (m, 8H), 1.30-1.72 (m, 8H); hLPA₁ IC₅₀ = 317 nM.

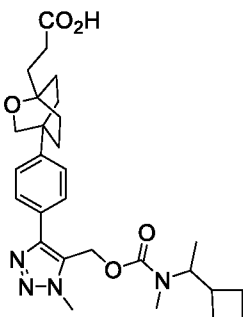
20

Example 4. 2-(4-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid



To a solution of Intermediate 14 (5.0 mg, 9.3 μ mol) in THF (1 mL) was added DIEA (9 μ L, 0.012 mmol) followed by N-methylcyclopentanamine (1.5 mg, 7 μ mol). The reaction mixture was stirred at RT for 18 h, after which aq. 2M LiOH (22 μ L, 0.022 mmol) was added. The reaction was stirred at RT for 18 h, then was concentrated *in vacuo*. The residue was dissolved in H₂O (1 mL), and the pH was adjusted with 1N aq. HCl to ~3 and extracted with EtOAc (2 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by 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 concentrated *in vacuo* by centrifugal evaporation to give the title compound (1.5 mg, 3.1 μ mol, 33% yield); [MS]⁺ = 482.4. ¹H NMR (400 MHz; DMSO-d₆) δ : 7.63 (s, 1H), 7.30-7.43 (m, 4H), 5.18 (s, 2H), 3.85-3.95 (m, 5H), 2.63-2.73 (m, 3H), 2.55 (s, 1H), 2.31 (s, 2H), 1.85-2.05 (m, 8H), 1.61 (br s, 4H), 1.47 (br s, 4H). hLPA₁ IC₅₀ = 1610 nM.

Example 5. ($\pm$)-3-(4-(4-(5-((((1-Cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)propanoic acid

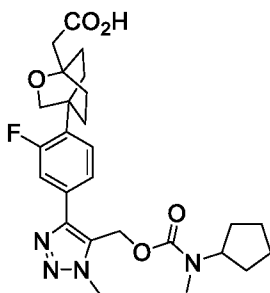


To a solution of Intermediate 15 (12 mg, 0.031 mmol) and DIPEA (0.022 mL, 0.125 mmol) in THF (0.5 mL) was added 4-nitrophenyl chloroformate (12.0 mg, 0.062 mmol). The reaction mixture was stirred at RT for 16 h, after which 1-cyclobutyl-N-methylmethanamine (3.09 mg, 0.031 mmol) was added. The reaction mixture was stirred for 1 h at RT, after which MeOH (0.3 mL) and 2N aq. LiOH (0.5 mL) were added, and the mixture was heated at 50 °C for 30 min, then was cooled to RT. 3N aq. HCl (0.5 mL) was added to mixture, which was concentrated in *vacuo*. The residue was purified

by 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.

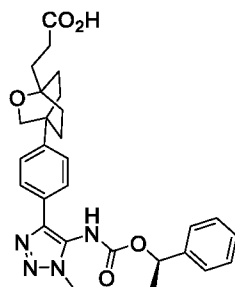
- 5 Fractions containing the desired product were combined and concentrated *in vacuo* by centrifugal evaporation to give the title compound (11 mg, 62.3% yield). LCMS [M + H]⁺ = 511.2; ¹H NMR (500 MHz, DMSO-d₆) δ 8.33 - 8.22 (m, 2H), 7.48 - 7.28 (m, 2H), 6.72 - 6.57 (m, 2H), 5.34 - 5.16 (m, 2H), 4.20 - 4.06 (m, 5H), 2.28 - 2.17 (m, 2H), 2.02 - 1.48 (m, 10H), 1.24 - 1.07 (m, 10H), 0.93 - 0.74 (m, 4H); hLPA₁ antagonist IC₅₀ = 440 nM.
- 10 nM.

Example 6. 2-(4-(4-(5-(((Cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid



- 15 Example 6 was prepared according to the general procedures described in Scheme 7 and for the synthesis of Example 5 by using 2-(4-(4-bromo-2-fluorophenyl)-2-oxabicyclo[2.2.2] octan-1-yl)acetic acid as the intermediate and N-methyl-cyclopentanamine instead of 1-cyclo-butyl-N-methylmethanamine. LCMS [M + H]⁺ = 501.2; ¹H NMR (DMSO-d₆) δ : 8.53-8.55 (m, 1H), 7.55-7.61 (m, 1H), 7.52 (dd, J=14.0, 1.7 Hz, 1H), 7.35 (t, J=8.4 Hz, 1H), 5.34 (s, 2H), 4.13 (s, 3H), 4.02 (s, 2H), 2.67 (s, 3H), 2.29 (s, 2H), 1.87-2.15 (m, 9H), 1.35-1.71 (m, 8H); hLPA₁ antagonist IC₅₀ = 363 nM.
- 20

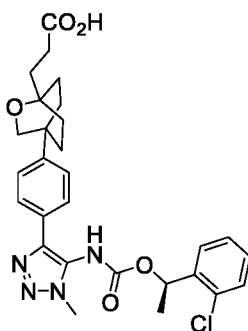
Example 7. 3-(4-(4-(1-methyl-5-(((R)-1-phenylethoxy)carbonyl)amino)-1H-1,2,3-triazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)propanoic acid



A mixture of Intermediate 16 (6 mg, 0.015 mmol), (PhO)₂PON₃ (16 μ L, 0.075 mmol), (R)-1-phenylethanol (2 mg, 0.016 mmol) and Et₃N (20 μ L, 0.15 mmol) in toluene (1 mL) was stirred at 65 °C for 2 h, then was cooled to RT and concentrated in vacuo.

- 5 The crude product was dissolved in THF (1 mL) and 2N aq. LiOH (0.5 mL) and stirred for 1 h at RT. 3M aq. HCl (0.5 mL) was added, and the mixture was concentrated in vacuo. The residue was purified by 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
- 10 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 concentrated *in vacuo* by centrifugal evaporation to give the title compound (1 mg, 13% yield). LCMS [M + H]⁺ = 505.2; ¹H NMR (500 MHz, DMSO-d₆) δ 7.69 - 7.52 (m, 2H), 7.49 - 7.35 (m, 2H), 7.33 - 7.13 (m, 5H), 5.27 - 4.96 (m, 2H), 3.73 - 3.41 (m, 4H), 2.03 -
- 15 1.84 (m, 5H), 1.86 - 1.64 (m, 2H), 1.51 - 1.33 (m, 2H), 1.38 - 1.18 (m, 2H), 1.06 - 0.78 (m, 6H); hLPA₁ IC₅₀ = 264 nM.

Example 8. 3-(4-(4-(5-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1-methyl-1H-1,2,3-triazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)propanoic acid

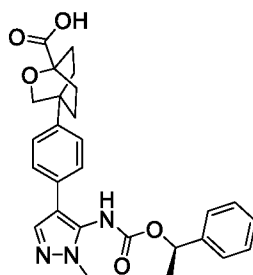


20

Example 8 was prepared according to the procedure used for the synthesis of Example 7 by using (R)-1-(2-chlorophenyl)ethan-1-ol as the alcohol in the Curtius rearrangement reaction instead of (R)-1-phenylethanol. LCMS [M + H]⁺ = 539.2; ¹H

NMR (500 MHz, DMSO- d_6) δ 7.81 - 7.56 (m, 3H), 7.53 - 7.26 (m, 5H), 6.08 - 5.89 (m, 1H), 3.71 - 3.45 (m, 3H), 2.35 - 2.18 (m, 3H), 2.09 - 1.76 (m, 8H), 1.73 - 1.41 (m, 7H); hLPA₁ IC₅₀ = 418 nM.

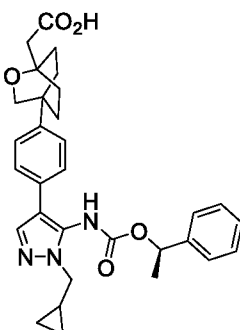
- 5 Example 9. (R)-4-(4-(1-methyl-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid



Example 9 was synthesized according to the procedures/synthetic sequence described for the synthesis of Examples 1 and 2, but using Intermediate 17 instead of

- 10 Intermediate 1. LCMS $[M + H]^+ = 501.2$; ^1H NMR (DMSO- d_6) δ : 8.53-8.55 (m, 1H), 7.55-7.61 (m, 1H), 7.52 (dd, $J=14.0$, 1.7 Hz, 1H), 7.35 (t, $J=8.4$ Hz, 1H), 5.34 (s, 2H), 4.13 (s, 3H), 4.02 (s, 2H), 2.67 (s, 3H), 2.29 (s, 2H), 1.87-2.15 (m, 9H), 1.35-1.71 (m, 8H); hLPA₁ IC₅₀ = 278 nM.

- 15 Example 10. (R)-2-(4-(4-(1-(cyclopropylmethyl)-5-(((1-phenylethoxy)carbonyl)amino)-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid



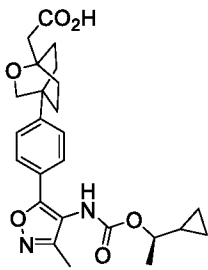
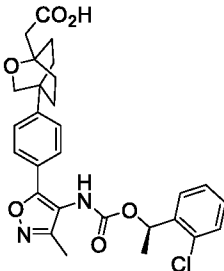
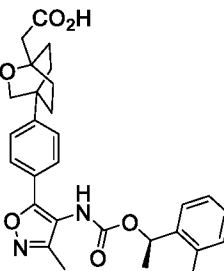
Example 10 was prepared from the bromo-pyrazole N-carbamate intermediate 18 and Intermediate 1 according to the synthetic sequence described for the synthesis of

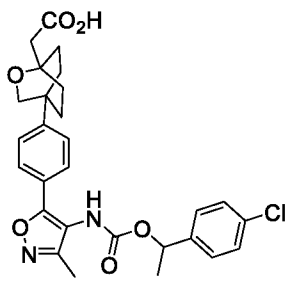
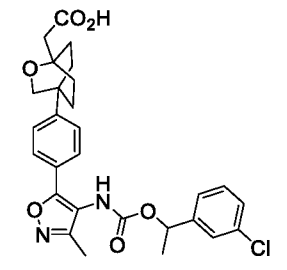
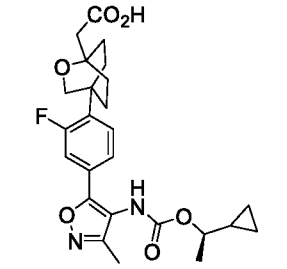
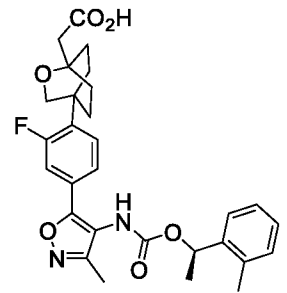
- 20 Example 2 (as well as Scheme 2). LCMS $[M + H]^+ = 530.2$; ^1H NMR (500 MHz, DMSO- d_6) δ 9.61 - 9.41 (m, 1H), 7.85 - 7.64 (m, 1H), 7.50 - 7.32 (m, 6H), 7.26 - 7.16 (m, 2H), 5.81 - 5.67 (m, 1H), 3.82 - 3.66 (m, 2H), 3.49 - 3.38 (m, 1H), 2.42 - 2.25 (m, 3H),

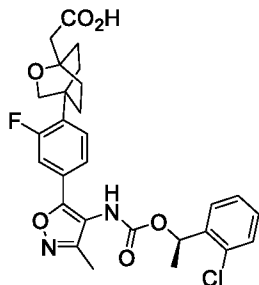
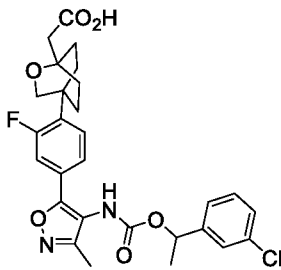
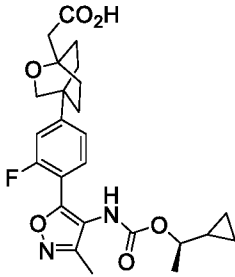
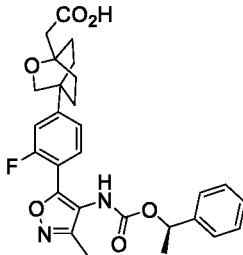
2.06 - 1.74 (m, 9H), 1.64 - 1.44 (m, 3H), 1.21 - 1.01 (m, 2H), 0.59 - 0.40 (m, 2H), 0.36 - 0.21 (m, 2H); hLPA₁ IC₅₀ = 422 nM.

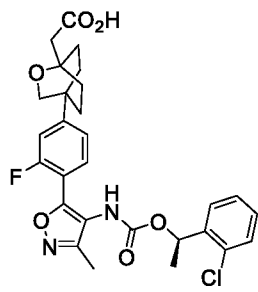
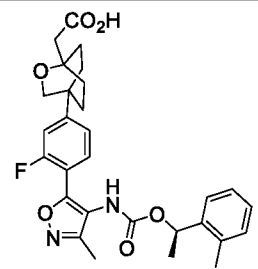
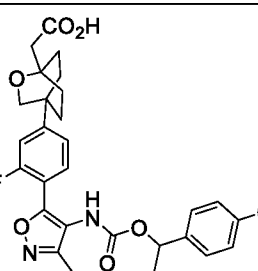
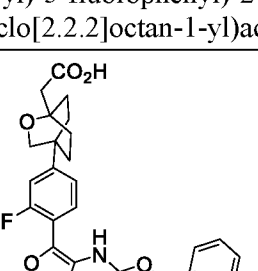
The compounds listed in Table 1 were prepared using the same general synthetic methods as described for the synthesis of respective Example indicated using the appropriate intermediates as described above (Schemes 1 and 6).

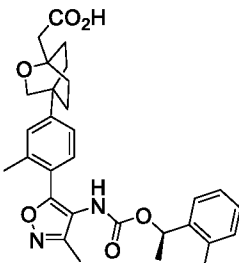
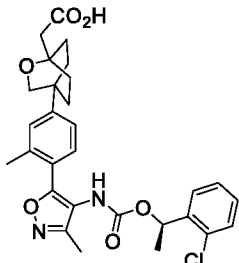
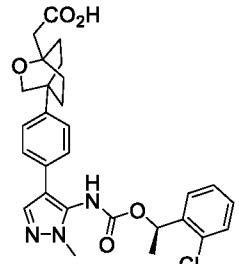
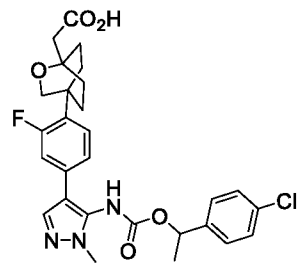
Table 1

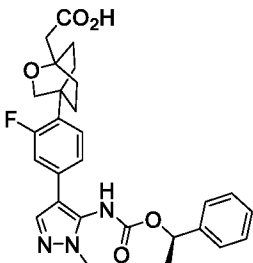
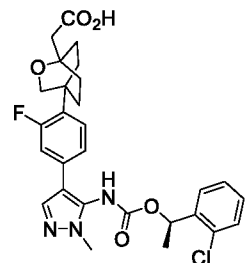
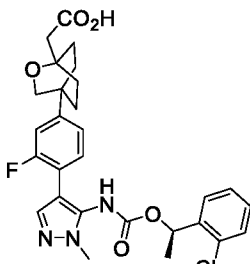
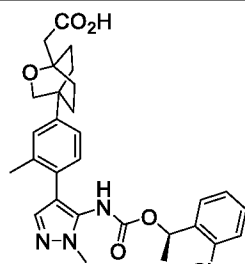
Ex #	Structure & Name	Analytical & Biological Data	Method
11	 2-(4-(4-(4-(((R)-1-cyclopropylethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS [M + H]⁺ = 455.1; ¹H NMR (DMSO-d₆) δ: 8.91-9.29 (m, 1H), 7.72 (br d, 2H), 7.50 (br d, 2H), 4.20 (br s, 1H), 3.90 (s, 2H), 3.60 (br d, 2H), 2.33 (s, 2H), 2.15 (br s, 3H), 1.80-2.06 (m, 8H), 1.30 (br s, 2H), 0.06-1.12 (m, 5H); hLPA₁ IC₅₀ = 194 nM.	Example 1
12	 2-(4-(4-(4-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS [M + H]⁺ = 525.1; ¹H NMR (DMSO-d₆) δ: 9.27-9.44 (m, 1H), 7.56-7.76 (m, 3H), 7.33-7.53 (m, 5H), 5.83-6.09 (m, 1H), 3.90 (s, 2H), 3.42-3.68 (m, 2H), 2.34 (s, 2H), 2.11 (br s, 2H), 2.00 (br d, 4H), 1.81-1.94 (m, 4H), 1.20-1.64 (m, 3H); hLPA₁ IC₅₀ = 72 nM.	Example 1
13	 2-(4-(4-(3-methyl-4-(((R)-1-(o-tolyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS [M + H]⁺ = 505.2; ¹H NMR (DMSO-d₆) δ: 9.25 (br s, 1H), 7.64 (br d, 2H), 7.03-7.52 (m, 6H), 5.87 (br d, 1H), 3.89 (s, 2H), 3.33-3.62 (m, 1H), 2.33 (br d, 5H), 2.09 (br s, 3H), 1.81-2.04 (m, 8H), 1.51 (br d, 3H); hLPA₁ IC₅₀ = 184 nM.	Example 1

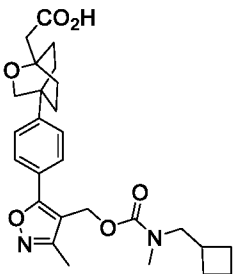
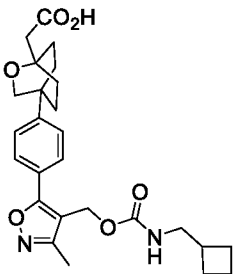
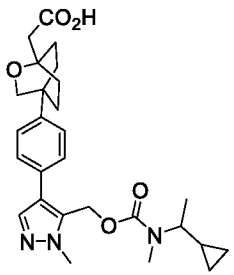
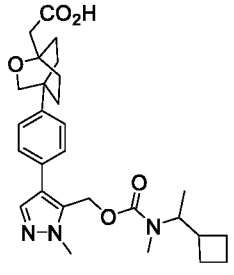
	acetic acid		
14	 (±)-2-(4-(2-fluoro-4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 525.0$; ^1H NMR (DMSO-d_6) δ: 9.16-9.39 (m, 1H), 7.58 (br d, $J=7.6$ Hz, 2H), 7.31-7.53 (m, 6H), 5.69 (br d, $J=6.4$ Hz, 1H), 3.88 (s, 2H), 2.33 (s, 2H), 2.10 (br s, 3H), 1.95-2.02 (m, 4H), 1.84-1.92 (m, 4H), 1.51 (br d, $J=5.5$ Hz, 3H); hLPA₁ IC₅₀ = 117 nM.	Example 1
15	 (±)-2-(4-(4-(4-(((1-(3-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 525.3$; ^1H NMR (DMSO-d_6) δ: 9.31 (br s, 1H), 7.65 (br d, $J=7.3$ Hz, 2H), 7.36-7.51 (m, 6H), 5.73 (br d, $J=5.5$ Hz, 1H), 3.89 (s, 2H), 2.34 (s, 2H), 2.12 (br s, 3H), 1.99 (br d, $J=10.1$ Hz, 4H), 1.85-1.93 (m, 4H), 1.53 (br d, $J=5.8$ Hz, 3H); hLPA₁ IC₅₀ = 379 nM.	Example 1
16	 2-(4-(4-(4-(((R)-1-cyclopropylethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M+H]^+ = 473.1$; ^1H NMR (DMSO-d_6) δ: 9.05-9.34 (m, 1H), 7.64 (br d, 1H), 7.56 (br d, 1H), 7.49 (br m, 1H), 4.27 (br s, 1H), 4.08 (s, 2H), 3.65 (br s, 2H), 2.40 (s, 2H), 2.23 (br s, 3H), 2.01-2.18 (m, 5H), 1.90-2.00 (m, 2H), 1.12 (br s, 1H), 1.37 (br s, 3H), 0.27-0.71 (m, 3H); hLPA₁ IC₅₀ = 407 nM.	Example 1
17	 2-(4-(2-fluoro-4-(3-methyl-4-(((R)-1-(o-tolyl)ethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 523.1$; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.34 (br s, 1H), 7.41-7.55 (m, 3H), 7.14-7.37 (m, 4H), 5.88 (br d, 1H), 4.00 (s, 2H), 2.27-2.39 (m, 5H), 2.11 (br s, 3H), 2.02 (br s, 6H), 1.85-1.93 (m, 2H), 1.52 (br d, 3H); hLPA₁ IC₅₀ = 119 nM.	Example 1

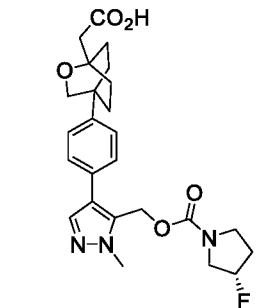
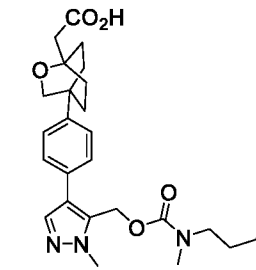
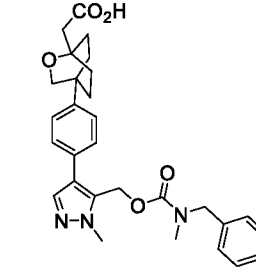
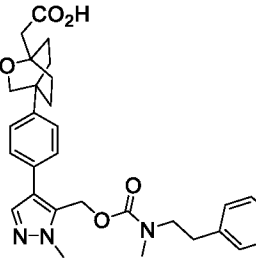
	isoxazol-5-yl)phenyl)-2-oxabicyclo [2.2.2]octan-1-yl)acetic acid		
18	 2-(4-(4-(4-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 543.2$; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.24-9.78 (m, 1H), 7.26-7.67 (m, 7H), 5.97 (br d, $J=6.4$ Hz, 1H), 4.00 (s, 2H), 2.34 (s, 2H), 2.12 (br s, 3H), 1.94-2.07 (m, 6H), 1.84-1.92 (m, 2H), 1.54 (br d, $J=5.2$ Hz, 3H); hLPA₁ IC₅₀ = 56 nM.	Example 1
19	 (±)-2-(4-(4-(4-(((1-(3-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 543.3$; ^1H NMR (DMSO-d_6) δ: 9.36-9.44 (m, 1H), 7.27-7.56 (m, 7H), 5.73 (br d, $J=5.8$ Hz, 1H), 4.00 (s, 2H), 2.33 (s, 2H), 2.13 (br s, 3H), 1.96-2.05 (m, 6H), 1.84-1.94 (m, 2H), 1.53 (br s, 3H); hLPA₁ IC₅₀ = 692 nM.	Example 1
20	 2-(4-(4-(4-(((R)-1-cyclopropylethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-3-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 473.1$; ^1H NMR (DMSO-d_6) δ: 8.91-9.13 (m, 1H), 7.62 (m, 1H), 7.27-7.48 (m, 2H), 4.16 (br s, 1H), 3.91 (s, 2H), 2.34 (s, 2H), 2.20 (br s, 3H), 1.80-2.08 (m, 8H), 0.91-1.48 (m, 4H), -0.01-0.66 (m, 4H); hLPA₁ IC₅₀ = 863 nM.	Example 1
21	 2-(4-(3-fluoro-4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 509.1$; ^1H NMR (DMSO-d_6) δ: 8.96-9.44 (m, 1H), 7.53-7.64 (m, 1H), 7.20-7.46 (m, 7H), 5.70 (br d, 1H), 3.90 (s, 2H), 2.35 (s, 2H), 2.16 (s, 3H), 1.80-2.06 (m, 8H), 1.10-1.69 (m, 3H); hLPA₁ IC₅₀ = 95 nM.	Example 1

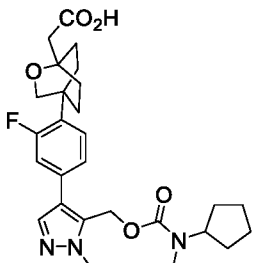
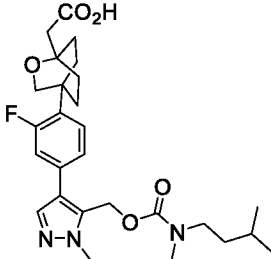
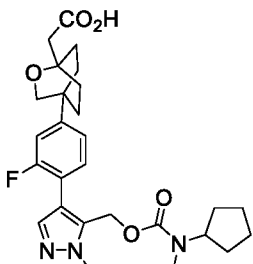
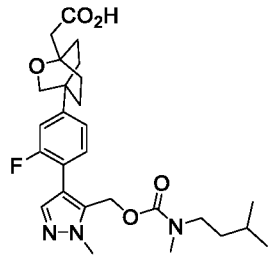
	[2.2.2]octan-1-yl)acetic acid		
22	 2-(4-(4-(4-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-3-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 543.3$; ^1H NMR (DMSO-d_6) δ: 9.19-9.46 (m, 1H), 7.23-7.73 (m, 7H), 5.93 (br d, 1H), 3.90 (s, 2H), 3.35 (br s, 1H), 2.35 (s, 2H), 2.16 (br s, 3H), 1.84-2.04 (m, 8H), 1.52 (br d, 2H); hLPA₁ IC₅₀ = 64 nM.	Example 1
23	 2-(4-(3-fluoro-4-(3-methyl-4-(((R)-1-(o-tolylethoxy)carbonyl) amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 523.1$; ^1H NMR (DMSO-d_6) δ: 9.17 (br s, 1H), 7.56 (br s, 1H), 7.12-7.48 (m, 6H), 5.84 (br s, 1H), 3.90 (s, 2H), 2.27-2.39 (m, 5H), 2.14 (br s, 3H), 1.87-2.05 (m, 8H), 1.49 (br d, 3H); hLPA₁ IC₅₀ = 98 nM.	Example 1
24	 (±)-2-(4-(4-(4-(((1-(4-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-3-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 542.9$; ^1H NMR (DMSO-d_6) δ: 9.09-9.38 (m, 1H), 7.56 (br d, J=7.3 Hz, 1H), 7.47 (br s, 2H), 7.40 (br d, J=7.3 Hz, 2H), 7.20-7.34 (m, 2H), 5.68 (br d, J=5.8 Hz, 1H), 3.91 (s, 2H), 2.35 (s, 2H), 2.17 (br s, 3H), 2.00 (br d, J=8.5 Hz, 4H), 1.84-1.95 (m, 4H), 1.50 (br d, J=5.2 Hz, 3H); hLPA₁ IC₅₀ = 406 nM.	Example 1
25	 (±)-2-(4-(4-(4-(((1-(3-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-3-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 543.0$; ^1H NMR (DMSO-d_6) δ: 9.11-9.49 (m, 1H), 7.58 (br d, J=7.0 Hz, 1H), 7.24-7.49 (m, 6H), 5.70 (br d, J=6.4 Hz, 1H), 3.90 (s, 2H), 2.35 (s, 2H), 2.17 (br s, 3H), 1.88-2.02 (m, 8H), 1.51 (br d, J=5.2 Hz, 3H); hLPA₁ IC₅₀ = 345 nM.	Example 1

26	 (±)-2-(4-(3-methyl-4-(3-methyl-4-(((R)-1-(o-tolyl)ethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-ylacetic acid	LCMS $[M + H]^+ = 519.2$; $^1\text{H NMR}$ (DMSO-d_6) δ: 9.02 (br s, 1H), 7.09-7.42 (m, 7H), 5.75-5.90 (m, 1H), 3.91 (s, 2H), 2.34 (s, 2H), 2.30 (br s, 2H), 2.24 (s, 4H), 2.12 (br s, 2H), 1.83-2.05 (m, 9H), 1.39-1.55 (m, 3H); hLPA₁ IC₅₀ = 92 nM.	Example 1
27	 2-(4-(4-(4-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-3-methylphenyl)-2-oxabicyclo[2.2.2]octan-1-ylacetic acid	LCMS $[M + H]^+ = 539.1$; $^1\text{H NMR}$ (DMSO-d_6) δ: 9.06-9.22 (m, 1H), 7.09-7.55 (m, 7H), 5.95 (br d, $J=6.1$ Hz, 1H), 3.91 (s, 2H), 2.34 (s, 3H), 2.25 (s, 3H), 2.13 (br s, 2H), 2.01 (br d, $J=6.4$ Hz, 4H), 1.85-1.96 (m, 4H), 1.50 (br d, $J=4.6$ Hz, 3H); hLPA₁ IC₅₀ = 185 nM.	Example 1
28	 2-(4-(4-(5-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-ylacetic acid	LCMS $[M + H]^+ = 524.0$; $^1\text{H NMR}$ (DMSO-d_6) δ: 9.13-9.91 (m, 1H), 7.72 (br s, 1H), 7.19-7.66 (m, 8H), 5.77-6.17 (m, 1H), 3.87 (s, 2H), 3.38-3.73 (m, 2H), 2.52 (br s, 2H), 2.34 (s, 2H), 1.99 (br d, 4H), 1.88 (br d, 4H), 1.09-1.71 (m, 3H); hLPA₁ IC₅₀ = 164 nM.	Example 2
29	 (±)-2-(4-(4-(5-(((1-(4-chlorophenyl)ethoxy)carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-ylacetic acid	LCMS $[M + H]^+ = 542.1$; $^1\text{H NMR}$ (DMSO-d_6) δ: 7.68-7.87 (m, 1H), 7.40 (br s, 4H), 7.02-7.25 (m, 4H), 5.49-5.86 (m, 1H), 2.17-2.28 (m, 3H), 1.87-2.03 (m, 11H), 1.50 (br s, 3H), 1.17-1.25 (m, 1H); hLPA₁ IC₅₀ = 1140 nM.	Example 2

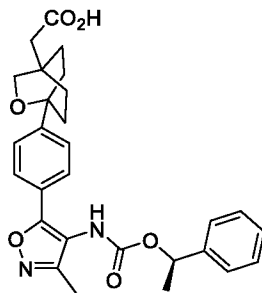
30	 2-(4-(2-fluoro-4-(1-methyl-5-((((R)-1-phenylethoxy)carbonyl)amino)-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 508.2$; ^1H NMR (DMSO-d_6) δ: 7.74-7.93 (m, 1H), 6.91-7.56 (m, 7H), 5.76 (br s, 1H), 3.95 (s, 2H), 3.62 (s, 2H), 3.35-3.47 (m, 3H), 2.09-2.21 (m, 2H), 1.76-2.23 (m, 7H), 1.16-1.68 (m, 3H); hLPA₁ IC₅₀ = 365 nM.	Example 2
31	 2-(4-(4-(5-((((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 542.1$; ^1H NMR (500MHz, DMSO-d_6) δ: 9.73 (br. s., 1H), 7.81 (br. s., 1H), 7.60 (br. s., 1H), 7.55 - 7.34 (m, 3H), 7.31 - 7.10 (m, 3H), 6.01 (br. s., 1H), 3.99 (s, 2H), 3.63 (br. s., 3H), 3.35 (br. s., 1H), 2.34 (s, 2H), 2.14 - 1.81 (m, 8H), 1.57 (br. s., 3H); hLPA₁ IC₅₀ = 112 nM.	Example 2
32	 2-(4-(4-(5-((((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-3-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 542.1$; ^1H NMR ^1H NMR (DMSO-d_6) δ: 9.22-9.76 (m, 1H), 7.26-7.69 (m, 5H), 6.99-7.24 (m, 2H), 5.86-6.09 (m, 1H), 3.88 (s, 2H), 3.65 (br s, 1H), 3.20-3.76 (m, 3H), 2.34 (s, 2H), 1.72-2.13 (m, 8H), 1.02-1.66 (m, 3H); hLPA₁ IC₅₀ = 115 nM.	Example 2
33	 2-(4-(4-(5-((((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-1-methyl-1H-pyrazol-4-yl)-3-methylphenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 538.1$; ^1H NMR (DMSO-d_6) δ: 9.33-9.76 (m, 1H), 7.48 (br s, 2H), 7.40 (br d, J=10.1 Hz, 1H), 7.25 (br s, 1H), 7.20 (br s, 1H), 7.14 (br s, 1H), 7.00-7.10 (m, 2H), 5.74-6.11 (m, 1H), 3.88 (s, 2H), 3.63 (br s, 3H), 2.34 (s, 2H), 2.19 (br s, 3H), 1.79-2.04 (m, 8H), 1.09-1.65 (m, 3H); hLPA₁ IC₅₀ = 537 nM.	Example 2

34	 2-(4-(4-(4-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 497.2$; ^1H NMR (DMSO-d_6) δ: 7.80 (br d, $J=7.9$ Hz, 1H), 7.73 (br d, $J=7.9$ Hz, 1H), 7.55 (br t, $J=7.9$ Hz, 2H), 5.01-5.14 (m, 2H), 4.04-3.8 (br d, $J=9.5$ Hz, 1H), 3.92 (s, 2H), 2.58 (br s, 2H), 2.26-2.39 (m, 6H), 1.85-2.06 (m, 9H), 1.62-1.84 (m, 3H), 1.42-1.60 (m, 2H), 1.18-1.39 (m, 1H), 0.74-1.00 (m, 3H); hLPA₁ IC₅₀ = 158 nM.	Example 3
35	 2-(4-(4-(4-2-(4-(4-(4-(((cyclobutylmethyl) carbamoyl)oxy)methyl)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 483.4$, ^1H NMR (DMSO-d_6) δ: 7.76 (br s, 2H), 7.61 (s, 2H), 5.07 (br s, 2H), 3.93 (s, 2H), 3.11 (br d, $J=6.4$ Hz, 2H), 2.77 (br s, 3H), 2.34 (br d, $J=5.5$ Hz, 5H), 1.98-2.04 (m, 4H), 1.88-1.97 (m, 4H), 1.79-1.88 (m, 2H), 1.59-1.74 (m, 2H), 1.45-1.76 (m, 3H); hLPA₁ IC₅₀ = 655.3 nM	Example 3
36	 (rac)-2-(4-(4-(5-(((1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 482.4$; ^1H NMR (DMSO-d_6) δ: 7.51 (br s, 1H), 7.24 (br s, 4H), 5.05 (s, 2H), 3.11-3.27 (m, 1H), 2.63 (br s, 3H), 2.42 (s, 4H), 2.20 (br s, 2H), 1.61-2.00 (m, 8H), 0.71-1.17 (m, 5H), -0.33-0.46 (m, 4H); hLPA₁ IC₅₀ = 1890 nM.	Example 4
37	 (rac)-2-(4-(4-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 496.3$; ^1H NMR (DMSO-d_6) δ: 7.65 (br d, $J=16.5$ Hz, 1H), 7.40-7.47 (m, 1H), 7.37 (br s, 3H), 5.20 (br d, $J=8.9$ Hz, 2H), 4.00-4.13 (m, 1H), 3.92 (br s, 1H), 2.54-2.67 (m, 6H), 2.33 (s, 3H), 1.35-1.79 (m, 1H), 1.34-2.10 (m, 14H), 0.80-1.00 (m, 3H); hLPA₁ IC₅₀ = 166 nM.	Example 4

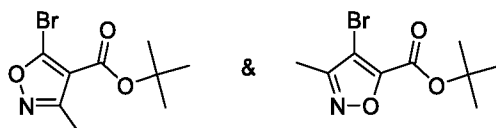
38	 2-(4-(4-(5-(((S)-3-fluoropyrrolidin-1-yl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo [2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 494.3$; ^1H NMR (DMSO-d_6) δ: 7.63 (br s, 1H), 7.39 (br s, 4H), 5.35 (br s, 1H), 5.10-5.28 (m, 3H), 3.92 (br s, 3H), 3.42-3.67 (m, 2H), 2.55 (br s, 2H), 2.33 (br s, 2H), 1.76-2.21 (m, 11H); hLPA₁ IC₅₀ = 1900 nM.	Example 4
39	 2-(4-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo [2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 484.2$; ^1H NMR (400 MHz, CDCl₃) δ 9.70 - 8.52 (m, 1H), 7.56 (s, 1H), 7.37 - 7.28 (m, 2H), 7.25 - 7.15 (m, 2H), 5.12 (s, 2H), 4.04 (s, 2H), 3.92 (s, 3H), 3.32 - 3.07 (m, 2H), 2.94 - 2.70 (m, 3H), 2.48 (s, 2H), 2.16 - 1.71 (m, 8H), 1.59 - 1.23 (m, 3H), 0.95 - 0.71 (m, 6H); hLPA₁ IC₅₀ = 520 nM.	Example 4
40	 2-(4-(4-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo [2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 504.2$; ^1H NMR (DMSO-d_6) δ: 7.63 (br d, J=8.5 Hz, 1H), 7.18-7.47 (m, 8H), 7.11 (br d, J=5.9 Hz, 1H), 5.08-5.37 (m, 2H), 4.32-4.46 (m, 2H), 3.74-4.00 (m, 3H), 2.79-2.91 (m, 2H), 2.73 (s, 2H), 2.29 (s, 2H), 1.77-2.02 (m, 9H); hLPA₁ IC₅₀ = 767 nM.	Example 4
41	 2-(4-(4-(5-(((4-chlorophenethyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 538.2$; ^1H NMR (DMSO-d_6) δ: 7.62 (s, 1H), 7.43 (br t, J=5.3 Hz, 1H), 7.35 (s, 3H), 7.31 (br d, J=8.2 Hz, 2H), 7.21 (br d, J=8.0 Hz, 2H), 5.07 (s, 2H), 3.88 (s, 2H), 3.46-3.64 (m, 1H), 3.22 (br d, J=6.3 Hz, 2H), 2.65-2.77 (m, 2H), 2.55 (s, 1H), 2.30 (s, 2H), 1.80-2.11 (m, 9H); hLPA₁ IC₅₀ = 2790 nM.	Example 4

42	 2-(4-(4-(5-(((cyclopentyl(methyl) carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 500.4$; $^1\text{H NMR}$ (DMSO-d_6) δ: 7.71 (s, 1H), 7.23-7.31 (m, 3H), 5.22 (s, 2H), 3.92 (s, 3H), 2.69 (br s, 3H), 2.34 (s, 3H), 1.96-2.13 (m, 6H), 1.83-1.94 (m, 2H), 1.79 (br s, 1H), 1.56-1.73 (m, 4H), 1.47 (br s, 5H); hLPA₁ IC₅₀ = 232 nM.	Example 4
43	 2-(4-(2-fluoro-4-(5-(((isopentyl(methyl) carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 502.4$; $^1\text{H NMR}$ (DMSO-d_6) δ: 7.73 (br d, $J=10.7$ Hz, 1H), 7.26 (br d, $J=5.8$ Hz, 3H), 5.22 (br d, $J=6.7$ Hz, 2H), 4.01 (br s, 2H), 3.92 (s, 3H), 3.04-3.42 (m, 2H), 2.75-2.89 (m, 3H), 2.34 (s, 2H), 1.95-2.12 (m, 6H), 1.81-1.94 (m, 2H), 1.21-1.54 (m, 3H), 0.70-0.98 (m, 6H); hLPA₁ IC₅₀ = 271 nM.	Example 4
44	 2-(4-(4-(5-(((cyclopentyl(methyl) carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)-3-fluorophenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 500.0$; $^1\text{H NMR}$ (DMSO-d_6) δ: 7.56 (s, 1H), 7.36 (br t, $J=8.1$ Hz, 1H), 7.17-7.29 (m, 2H), 6.29-6.33 (m, 1H), 5.12 (s, 2H), 4.10 (s, 1H), 3.91 (s, 3H), 2.61 (br s, 3H), 2.31-2.43 (m, 3H), 1.96-2.07 (m, 4H), 1.82-1.94 (m, 4H), 1.37-1.70 (m, 9H); hLPA₁ IC₅₀ = 1860 nM.	Example 4
45	 2-(4-(3-fluoro-4-(5-(((isopentyl(methyl) carbamoyl)oxy)methyl)-1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid	LCMS $[M + H]^+ = 502.1$; $^1\text{H NMR}$ (DMSO-d_6) δ: 7.52-7.61 (m, 1H), 7.36 (br d, $J=5.8$ Hz, 1H), 7.16-7.28 (m, 2H), 5.12 (br s, 2H), 3.90 (br d, $J=8.2$ Hz, 5H), 3.18 (br s, 1H), 3.07 (br s, 1H), 2.79 (br s, 1H), 2.67 (br s, 1H), 2.34 (s, 2H), 1.97-2.04 (m, 4H), 1.84-1.95 (m, 4H), 1.44-1.52 (m, 1H), 1.17-1.36 (m, 3H), 0.73-0.93 (m, 6H); hLPA₁ IC₅₀ = 1120 nM.	Example 4

Example 46. 2-(1-(4-(3-Methyl-5-((((R)-1-phenylethoxy)carbonyl)amino)isoxazol-4-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid

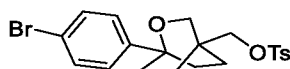


- 5 46A. tert-butyl 5-bromo-3-methylisoxazole-4-carboxylate and tert-butyl 4-bromo-3-methyl- isoxazole-5-carboxylate (mixture)



Aq. 6% NaOCl (70.2 mL, 68.3 mmol) was added to a solution of acetaldoxime (2.42 g, 41.0 mmol) and tert-butyl 3-bromopropiolate (5.60 g, 27.3 mmol) in DCM (100 mL) dropwise at RT over 2 h. The reaction was stirred at RT for 30 min, after which analytical HPLC showed starting material was still present. More acetaldoxime (2.42 g, 41.0 mmol) and 6% aq. NaOCl (70.2 mL, 68.3 mmol) were added and the reaction was stirred at RT until analytical HPLC showed that the reaction was complete. The organic phase was separated, washed with water and brine, dried (MgSO₄), and concentrated in vacuo. The crude product (an oil) was chromatographed (40 g SiO₂; continuous gradient from 0% to 30% EtOAc in hexane over 10 min) to give a mixture of the two isomeric title compounds (3.20 g, 12.2 mmol, 44.7% yield) as a clear oil.

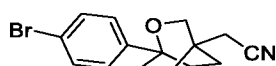
- 46B. (1-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-4-yl)methyl 4-methylbenzenesulfonate



A solution of 1.6 M nBuLi in hexane (8.0 mL, 12.8 mmol) was added dropwise to a -78 °C solution of 1,4-dibromobenzene (5.47 g, 23.2 mmol) in THF (25 mL). The reaction was stirred at -78 °C for 2 h, after which a solution of (4-oxocyclohexane-1,1-diyl)bis(methylene) bis(4-methylbenzenesulfonate; synthesized according to Example 1E,

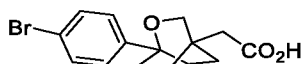
page 55 in US Patent 8,962,660; 5.1 g, 10.9 mmol) in THF (20 mL) was added. The reaction mixture was allowed to slowly warm to RT over 1 h and stirred at RT for another 1 h, after which LC-MS showed formation of the desired product. Powdered NaOH (2.19 g, 54.7 mmol) was carefully added. The reaction mixture was heated at reflux under N₂ for 18 h, then was cooled to RT and partitioned between EtOAc and water (50 mL each). The organic layer was washed with water (50 mL x 3), dried (MgSO₄), and partially concentrated in vacuo. The solid precipitate was collected by filtration to give the title compound (3.70 g, 8.20 mmol, 75 % yield) as an off- white solid. LCMS [M + H]⁺ = 450.9/452.9; ¹H NMR (CDCl₃) δ: 7.81 - 7.75 (m, 2H), 7.44 - 7.39 (m, 2H), 7.36 (dt, J = 8.2, 0.8 Hz, 2H), 7.25 - 7.20 (m, 2H), 3.81 (t, J = 1.5 Hz, 2H), 3.75 (s, 2H), 2.46 (s, 3H), 1.98 (t, J = 8.0 Hz, 4H), 1.81 - 1.57 (m, 4H).

46C. 2-(1-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetonitrile



A mixture of compound 46B (3.70 g, 8.20 mmol), NaCN (1.47 g, 30.0 mmol), and a catalytic amount of KI in DMSO (10 mL) was stirred at 80 °C for 18 h, then was cooled to RT. Analytical HPLC showed that the reaction was complete. The reaction mixture was partitioned between EtOAc and water (50 mL each). The organic layer was washed with 1N aq. NaOH (x1), water (x3), dried (MgSO₄), and concentrated in vacuo to give the title compound (2.50 g, 8.16 mmol, 100 % yield) as an off-white solid. LCMS [M + Na]⁺ = 360.9/362.9; ¹H NMR (CDCl₃) δ: 7.46 - 7.41 (m, 2H), 7.28 - 7.23 (m, 2H), 3.93 (t, J = 1.4 Hz, 2H), 2.23 (s, 2H), 2.11 - 1.99 (m, 4H), 1.91 - 1.78 (m, 4H).

46D. 2-(1-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid

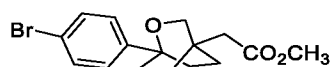


A mixture of compound 46C (2.50 g, 8.16 mmol) and 40% aq. KOH (5.75 mL, 40.8 mmol) in ethylene glycol (20 mL) was stirred at 120 °C for 18 h, then was cooled to RT. Analytical HPLC showed that the reaction was complete. The reaction mixture was partially concentrated in vacuo. The remaining solution was diluted with water (200 mL), then was acidified to pH = 2 with conc. HCl at 0 °C. The mixture was filtered, and the collected solids were washed with water until the filtrate was neutral. The solids were

dried in vacuo to give the title compound (2.58 g, 7.93 mmol, 97 % yield) as a white solid. LCMS $[M - H]^+ = 323.1/325.1$; ^1H NMR (DMSO- d_6) δ : 12.13 (s, 1H), 7.51 - 7.45 (m, 2H), 7.35 - 7.30 (m, 2H), 3.84 (t, $J = 1.4$ Hz, 2H), 2.11 - 2.00 (m, 4H), 1.85 - 1.65 (m, 6H).

5

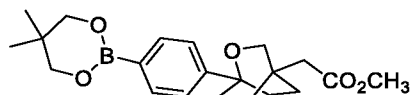
46E. Methyl 2-(1-(4-bromophenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetate



A solution of 2.0 M TMSCHN₂ in hexane (7.69 mL, 15.38 mmol) was added to a solution of compound 46D (2.50 g, 7.69 mmol) in THF (10 mL)/MeOH (5 mL) at 0 °C.

10 The reaction mixture was allowed to warm to RT and stirred at RT for 2 h, then was concentrated in vacuo. The crude oil was chromatographed (40 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (2.5 g, 7.37 mmol, 96 % yield) as a white solid. $[M + Na]^+ = 360.9/362.9$; ^1H NMR (CDCl₃) δ : 7.44 - 7.40 (m, 2H), 7.28 - 7.24 (m, 2H), 3.93 (t, $J = 1.3$ Hz, 2H), 3.67 (s, 3H), 2.18 (s, 15 2H), 2.06 - 1.95 (m, 4H), 1.86 - 1.73 (m, 4H).

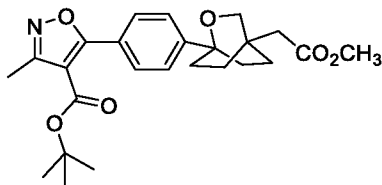
46F. Methyl 2-(1-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetate



20 A mixture of PdCl₂(dppf) (101 mg, 0.139 mmol), bis(pinacolato)diboron (438 mg, 1.94 mmol), KOAc (218 mg, 2.22 mmol), and compound 46E (470 mg, 1.39 mmol) in anhydrous DMSO (10 mL) was degassed under Ar. The reaction mixture was stirred at 80 °C under Ar for 2 h, then was cooled to RT and poured into cold 1N aq. HCl (20 mL) and extracted with EtOAc (3 x). The combined organic extracts were washed with brine 25 (2 x), dried (Na₂SO₄) and concentrated in vacuo. The crude oil was chromatographed (24 g SiO₂; continuous gradient from 0% to 30% EtOAc in hexane over 10 min) to give the title compound (418 mg, 1.12 mmol, 81 % yield) as an off-white solid. ^1H NMR (CDCl₃) δ : 7.74 (d, $J=8.3$ Hz, 2H), 7.37 (d, $J=8.3$ Hz, 2H), 3.94 (s, 2H), 3.75 (s, 4H), 3.67 (s, 3H), 2.18 (s, 2H), 2.10 - 1.99 (m, 4H), 1.85 - 1.73 (m, 4H), 1.01 (s, 6H)

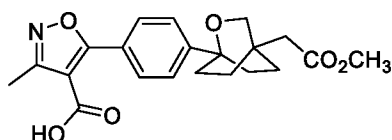
30

46G. tert-butyl 5-(4-(4-(2-methoxy-2-oxoethyl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)-3-methylisoxazole-4-carboxylate



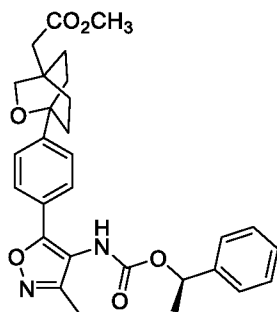
A mixture of compound 46A (93 mg, 0.355 mmol), compound 46F (110 mg, 0.295 mmol), (Ph₃P)₂Pd(II)Cl₂ (21 mg, 0.030 mmol), and K₂CO₃ (123 mg, 0.89 mmol) in DME (8 mL) was degassed under Ar, then was stirred at 80 °C for 4 h and cooled to RT. The reaction mixture was acidified with 1N aq. HCl and extracted with EtOAc. The organic layer was washed with water and concentrated in vacuo. The crude product (an oil) was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (20 mg, 0.045 mmol, 15.3 % yield) as a light brownish oil. LCMS [M + H]⁺ = 442.1; ¹H NMR (CDCl₃) δ: 7.82 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 3.97 (s, 2H), 3.68 (s, 3H), 2.48 (s, 3H), 2.20 (s, 2H), 2.14 - 1.95 (m, 4H), 1.92 - 1.75 (m, 4H), 1.51 (s, 9H).

46H. 5-(4-(4-(2-methoxy-2-oxoethyl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)-3-methylisoxazole-4-carboxylic acid



A mixture of compound 46G (20 mg, 0.045 mmol) and formic acid (174 μL, 4.53 mmol) was stirred at RT for 18 h, then was concentrated in vacuo. The residue was dissolved in EtOAc, washed with water, dried (MgSO₄) and concentrated in vacuo to give the title compound (17 mg, 0.044 mmol, 97 % yield) as a light brownish solid. [M - H]⁺ = 384.3; ¹H NMR (CDCl₃) δ: 7.88 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 3.97 (s, 2H), 3.69 (s, 3H), 2.53 (s, 3H), 2.20 (s, 2H), 2.14 - 2.04 (m, 4H), 1.91 - 1.76 (m, 4H)

46I. Methyl 2-(1-(4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetate



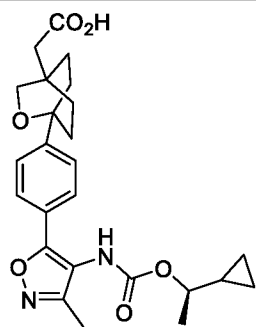
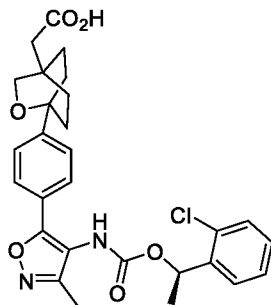
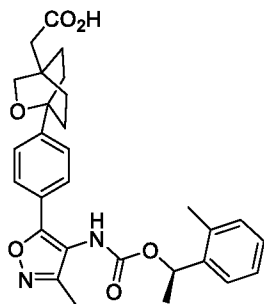
A mixture of compound 46H (17 mg, 0.044 mmol), (PhO)₂PON₃ (0.011 mL, 0.053 mmol), (R)-(+)-1-phenylethanol (5.4 μ L, 0.049 mmol), and TEA (8 μ L, 0.057 mmol) in toluene (1 mL) was stirred at 80 °C for 1 h, then was cooled to RT and concentrated in vacuo. The crude oily product was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (17 mg, 0.034 mmol, 76 % yield) as off white solid. LCMS [M + H]⁺ = 505.1; ¹H NMR (CDCl₃) δ : 7.82 - 7.01 (m, 9H), 6.71 - 5.75 (m, 2H), 4.02 - 3.92 (m, 2H), 3.74 - 3.64 (m, 3H), 2.27 - 2.13 (m, 5H), 2.04 (t, J = 8.0 Hz, 4H), 1.92 - 1.72 (m, 4H), 1.71 - 1.33 (m, 3H).

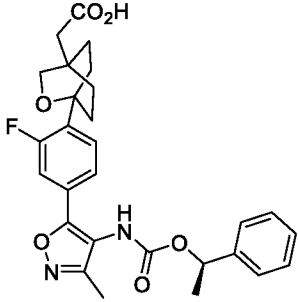
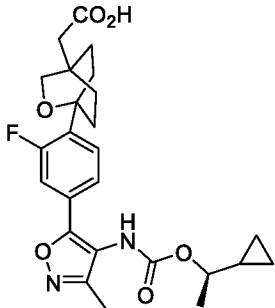
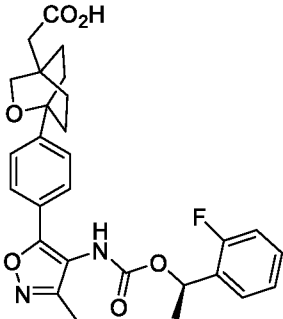
Example 46

A solution of compound 46I (17 mg, 0.034 mmol) and 1N aq. NaOH (0.34 mL, 0.34 mmol) in THF (0.5 mL)/MeOH (0.5 mL) was stirred at RT for 2 h, then was concentrated in vacuo. The residue was acidified to pH = 2 with 1N aq. HCl and then purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (11 mg, 0.021 mmol, 63.2 % yield) as a clear oil. LCMS [M - H]⁺ = 489.2; ¹H NMR (CDCl₃) δ : 7.83 - 7.05 (m, 9H), 6.20 - 5.79 (m, 1H), 3.98 (s, 2H), 2.28 - 2.14 (m, 5H), 2.06 (t, J = 7.9 Hz, 4H), 1.86 (q, J = 7.6, 7.0 Hz, 4H), 1.70 - 1.35 (m, 3H); hLPA₁ IC₅₀ = 190 nM.

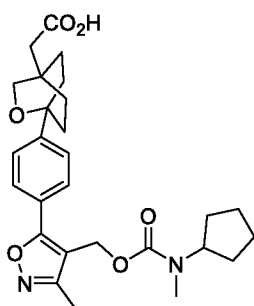
The compounds listed in Table 2 were prepared by using same synthetic sequence and the same intermediates as described for the synthesis of Example 46 (and also as described in the synthetic sequence shown in Scheme 3).

5 Table 2

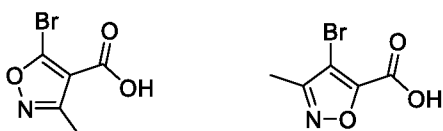
Ex #	Structure & Name	Analytical & Biological Data
47	 2-(1-(4-(4-(((R)-1-cyclopropylethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid	LCMS $[M + H]^+ = 455.5$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 2H), 7.31 (d, $J = 8.3$ Hz, 2H), 5.74 (s, 1H), 4.11 (s, 1H), 3.79 (s, 2H), 2.10 (s, 3H), 2.03 (s, 2H), 1.96 - 1.81 (m, 4H), 1.76 - 1.60 (m, 4H), 1.28 - 0.58 (m, 4H), 0.44 - 0.06 (m, 4H); hLPA₁ IC₅₀ = 583 nM.
48	 2-(1-(4-(4-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid	LCMS $[M + H]^+ = 525.4$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 - 7.62 (m, 2H), 7.57 - 6.96 (m, 7H), 6.21 (q, $J=6.5$ Hz, 1H), 3.97 (br. s., 2H), 2.30 - 2.14 (m, 5H), 2.11 - 1.99 (m, 4H), 1.91 - 1.77 (m, 4H), 1.68 - 1.37 (m, 3H); hLPA₁ IC₅₀ = 354 nM.
49	 2-(1-(4-(3-methyl-4-(((R)-1-(o-tolyl)ethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid	LCMS $[M - H]^+ = 503.4$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 - 7.58 (m, 2H), 7.55 - 7.36 (m, 3H), 7.31 - 6.96 (m, 4H), 6.20 - 6.00 (m, 1H), 3.97 (br. s., 2H), 2.45 - 2.27 (m, 3H), 2.26 - 2.17 (m, 5H), 2.09 - 2.01 (m, 4H), 1.85 (d, $J=6.9$ Hz, 4H), 1.65 - 1.35 (m, 3H); hLPA₁ IC₅₀ = 303 nM.

50	 2-(1-(2-fluoro-4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid	LCMS $[M - H]^+ = 507.1$; ^1H NMR (500 MHz, DMSO-d_6) δ 9.31 (br s, 1H), 7.74 - 6.97 (m, 8H), 5.73 (br s, 1H), 2.32 - 2.20 (m, 2H), 2.11 (br s, 5H), 1.91 - 1.66 (m, 6H), 1.53 (br s, 2H), 2 protons are in water suppression area; hLPA₁ IC₅₀ = 57 nM.
51	 2-(1-(4-(4-(((R)-1-cyclopropylethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-2-fluorophenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid	LCMS $[M + H]^+ = 473.1$; ^1H NMR (500 MHz, DMSO-d_6) δ 9.13 (br s, 1H), 7.70 (br t, $J=7.9$ Hz, 1H), 7.58 (br d, $J=7.9$ Hz, 1H), 7.50 (br d, $J=12.8$ Hz, 1H), 4.22 (br s, 1H), 2.55 (s, 2H), 2.27 (br t, $J=11.1$ Hz, 2H), 2.22 - 2.08 (m, 5H), 1.92 - 1.68 (m, 6H), 1.31 (br s, 2H), 1.07 (br s, 1H), 0.62 - 0.23 (m, 4H), 2 protons are in water suppression area; hLPA₁ IC₅₀ = 222 nM.
52	 2-(1-(4-(4-(((R)-1-(2-fluorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid	LCMS $[M - H]^+ = 507.4$; ^1H NMR (500 MHz, CDCl₃) δ 8.36 (br. s., 2H), 7.81 - 7.36 (m, 5H), 7.35 - 6.90 (m, 3H), 6.12 (q, $J=6.6$ Hz, 1H), 3.98 (br. s., 2H), 2.22 (d, $J=3.3$ Hz, 5H), 2.11 - 1.99 (m, 4H), 1.92 - 1.77 (m, 4H), 1.71 - 1.36 (m, 3H); ^{19}F NMR (471 MHz, CDCl₃) δ 118.05 (s), -118.49 (s); hLPA₁ IC₅₀ = 134 nM.

Example 53. 2-(1-(4-(4-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetic acid



53A. 5-bromo-3-methylisoxazole-4-carboxylic acid and 4-bromo-3-methylisoxazole-5-carboxylic acid (mixture)

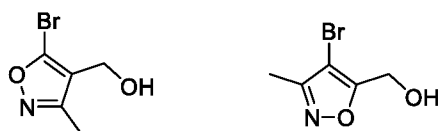


5

A solution of compound 46A (mixture of two isomers as described above; 1.00 g, 3.82 mmol) in TFA (0.88 mL, 11.5 mmol) and DCM was stirred at 50 °C for 2 h, then was cooled to RT and concentrated in vacuo to give a mixture of 5-bromo-3-methylisoxazole-4-carboxylic acid and 4-bromo-3-methylisoxazole-5-carboxylic acid (0.786 g, 3.82 mmol, 100 % yield) as a clear oil.

10

53B. mixture of 5-bromo-3-methylisoxazol-4-yl)methanol and (4-bromo-3-methylisoxazol-5-yl)methanol

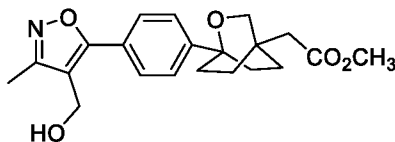


15

A solution of 1 M BH₃.THF in THF (2.77 mL, 2.77 mmol) was added to compound 53A (285 mg, 1.38 mmol) in THF (2 mL) at -20 °C. The reaction was allowed to warm to RT and stirred at RT for 18 h, then was concentrated in vacuo. The residue was dissolved in EtOAc and washed with water. The organic layer was concentrated in vacuo. The crude product (oil) was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 20% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (93 mg, 0.484 mmol, 35.0 % yield).

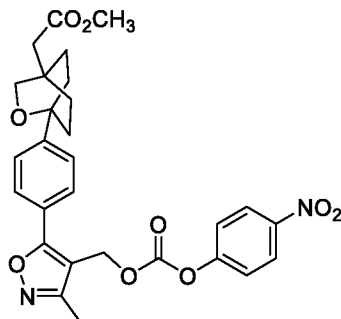
20

53C. methyl 2-(1-(4-(4-(hydroxymethyl)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetate



A mixture of Intermediate 1 (811 mg, 2.18 mmol), compound 53B (1.26 g, 4.79 mmol), Pd(Ph₃P)₄ (12 mg, 10.1 μmol), and K₂CO₃ (139 mg, 1.01 mmol) in DME (5 mL)/H₂O (0.2 mL) was degassed under Ar, then was stirred at 80 °C for 18 h and cooled to RT. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product (oil) was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (22 mg, 0.059 mmol, 29.4 % yield) as a light yellowish solid. LCMS [M + H]⁺ = 372.2; ¹H NMR (CDCl₃) δ 7.71 (d, *J*=8.6 Hz, 2H), 7.51 (d, *J*=8.6 Hz, 2H), 4.63 (s, 2H), 3.96 (s, 2H), 3.68 (s, 3H), 2.37 (s, 4H), 2.19 (s, 2H), 2.10 - 2.00 (m, 4H), 1.90 - 1.75 (m, 4H).

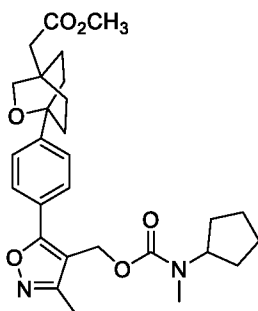
53D. methyl 2-(1-(4-(3-methyl-4-(((4-nitrophenoxy)carbonyl)oxy)methyl)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetate



A solution of 4-nitrophenyl chloroformate (24 mg, 0.12 mmol) in DCM (0.5 mL) was added to a solution of compound 53C (22 mg, 0.059 mmol) and iPr₂NEt (0.041 mL, 0.24 mmol) in DCM (1 mL). The reaction mixture was stirred at RT for 18 h, then was concentrated in vacuo. The crude oily product was chromatographed (4 g SiO₂; continuous gradient from 0% to 30% EtOAc in hexane over 10 min) to give the title compound (30 mg, 0.056 mmol, 94 % yield) as a light yellowish oil. ¹H NMR (CDCl₃) δ: 8.29 (d, *J* = 9.1 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 9.2

Hz, 2H), 5.20 (s, 2H), 3.90 (s, 2H), 3.62 (s, 3H), 2.37 (s, 3H), 2.14 (s, 2H), 2.09 - 1.94 (m, 4H), 1.83 - 1.69 (m, 4H).

53E. methyl 2-(1-(4-(4-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)acetate

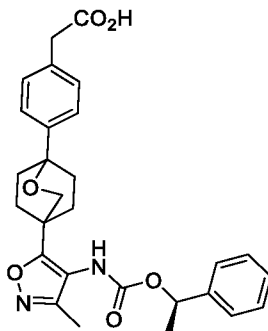


A mixture of compound 53D (30 mg, 0.056 mmol), cyclopentylmethylamine (0.020 mL, 0.17 mmol), and *i*Pr₂NEt (0.049 mL, 0.28 mmol) in THF (1 mL) was stirred at RT for 2 h and then concentrated in vacuo. The crude product was chromatographed (4 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (27 mg, 0.054 mmol, 97 % yield) as a clear oil. ¹H NMR (CDCl₃) δ 7.65 (d, *J*=8.3 Hz, 2H), 7.48 - 7.42 (m, 2H), 5.02 (s, 2H), 3.89 (s, 2H), 3.62 (s, 3H), 2.69 (br s, 3H), 2.32 (s, 3H), 2.13 (s, 2H), 2.06 - 1.94 (m, 4H), 1.83 - 1.35 (m, 13H).

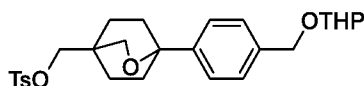
Example 53

A mixture of compound 53E (27 mg, 0.054 mmol) and 2.0 M aq. LiOH (0.27 mL, 0.54 mmol) in THF (0.5 mL)/MeOH (0.2 mL) was stirred at RT for 5 h, then was partitioned between EtOAc and 1N aq. HCl. The organic layer was washed with water and concentrated in vacuo. The crude product (oil) was purified by preparative HPLC (Column: XBridge C18, 19 x 200 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: 30-70% B over 25 min, then a 5-min hold at 100% B; Flow: 20 mL/min) to give the title compound (18.3 mg, 0.036 mmol, 66.3 % yield) as an oil. LCMS [M - H]⁺ = 481.05; ¹H NMR (DMSO-*d*₆) δ: 7.71 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 5.05 (s, 2H), 3.86 (s, 2H), 2.65 (s, 3H), 2.31 (s, 3H), 2.18 - 1.96 (m, 4H), 1.89 - 1.16 (m, 15H); hLPA₁ IC₅₀ = 2,552 nM.

Example 54. (R)-2-(4-(4-(3-methyl-4-(((1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)-2-oxabicyclo[2.2.2] octan-1-yl)phenyl)acetic acid

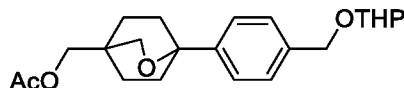


- 5 54A. (1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl) methyl 4-methylbenzenesulfonate



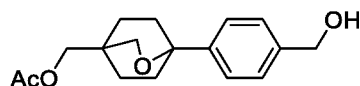
A solution of 1.6 M n-BuLi in hexane (8.0 mL, 12.8 mmol) was added dropwise to a solution of 2-(((4-bromobenzyl)oxy)tetrahydro-2H-pyran (7.0 g, 25.8 mmol) in THF (25 mL) at -78 °C. The reaction was stirred at -78 °C for 2 h, after which a solution of (4-oxocyclohexane-1,1-diyl)bis (methylene)bis(4-methylbenzenesulfonate) (synthesized according to compound 1E, page 55 in US Patent 8,962,660; 10.0 g, 21.4 mmol) in THF (50 mL) was added. The reaction mixture was allowed to slowly warm up to RT over 1 h and stirred at RT for 1 h. LC-MS showed the formation of the initial alcohol product from the ArLi addition. Powdered NaOH (4.29 g, 107 mmol) was added. The reaction mixture was heated at reflux under N₂ for 18 h, then was cooled to RT. The residue was partitioned between EtOAc (50 mL) and water. The organic layer was washed with water (50 mL x 3), dried (MgSO₄) and concentrated in vacuo. The crude product (an oil) was chromatographed (80 g SiO₂; continuous gradient from 0% to 20% EtOAc in hexane over 20 min) to give the title compound (4.80 g, 9.86 mmol, 46.0 % yield) as an off white solid. [M - OTHP]⁺ = 385.1; ¹H NMR (CDCl₃) δ: 7.80 (d, J = 8.3 Hz, 2H), 7.41 - 7.29 (m, 6H), 4.76 (d, J = 12.0 Hz, 1H), 4.69 (t, J = 3.6 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.92 (ddd, J = 11.6, 8.5, 3.1 Hz, 1H), 3.83 (t, J = 1.4 Hz, 2H), 3.76 (s, 2H), 3.58 - 3.50 (m, 1H), 2.47 (s, 3H), 2.02 (t, J = 8.0 Hz, 4H), 1.93 - 1.48 (m, 10H).

54B. (1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)methyl acetate



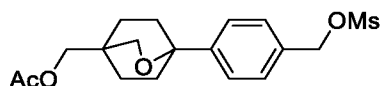
A mixture of compound 54A (2.72 g, 5.59 mmol) and NaOAc (2.29 g, 27.9 mmol) in DMSO (10 mL) was stirred at 80 °C for 8 days, then was cooled to RT and partitioned between EtOAc and water (50 mL each). The organic layer was washed with water, dried (MgSO₄), and concentrated in vacuo to give the crude title compound (2.0 g, 5.34 mmol, 96 % yield) as a light brownish oil. This material was used in the next reaction without further purification. [M - THPO]⁺ = 273.1.

54C. (1-(4-(hydroxymethyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)methyl acetate



A mixture of compound 54B (2.0 g, 5.34 mmol) and PPTS (0.134 g, 0.534 mmol) in MeOH (10 mL) was stirred at 50 °C for 5 h, then was cooled to RT and concentrated in vacuo. The crude oil was chromatographed (24 g SiO₂; continuous gradient from 0% to 50% EtOAc/ hexane over 10 min) to give the title compound (1.25 g, 4.31 mmol, 81 % yield) as a light yellowish solid. ¹H NMR (500 MHz, CDCl₃) δ 7.41 - 7.37 (m, 2H), 7.30 (d, *J*=8.3 Hz, 2H), 4.65 (s, 2H), 3.93 (s, 2H), 3.84 (s, 2H), 2.08 - 2.02 (m, 7H), 1.86 - 1.74 (m, 3H), 1.73 - 1.63 (m, 2H).

54D. (1-(4-(((methanesulfonyl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)methyl acetate

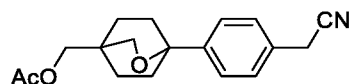


Methanesulfonyl chloride (0.403 mL, 5.17 mmol) was added dropwise to a solution of compound 54C (1.25 g, 4.31 mmol) and Et₃N (1.20 mL, 8.61 mmol) in DCM (10 mL) at 0 °C. The reaction was allowed to warm to RT and stirred at RT for 2 h. HPLC showed the reaction was complete at this point. The reaction mixture was concentrated in vacuo. The residue was partitioned between EtOAc and water (25 mL each). The organic layer was washed with 1N aq. HCl and water, dried (MgSO₄) and

concentrated in vacuo to give the title compound (1.58 g, 4.29 mmol, 100 % yield) as a yellowish oil. $[M - OAc]^+ = 309.4$.

54E. (1-(4-(cyanomethyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)methyl acetate

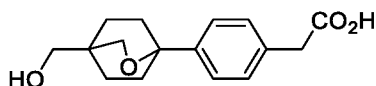
5



A mixture of compound 54D (1.58 g, 4.29 mmol) and NaCN (0.420 g, 8.58 mmol) in DMSO (10 mL) was stirred at 80 °C for 18 h, then was cooled to RT and partitioned between EtOAc and water (25 mL each). The organic layer was washed with water (2X) and concentrated in vacuo to give the crude title compound (1.284 g, 4.29 mmol, 100 % yield) as a yellowish oil. This crude material was used in the next reaction without further purification. $[M + H]^+ = 300.4$.

10

54F. 2-(4-(4-(hydroxymethyl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)acetic acid

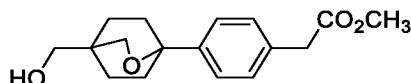


15

A mixture of compound 54E and aq. 30% NaOH (2.86 g, 21.5 mmol) in EtOH (10 mL) was stirred under reflux for 30 h, then was cooled to RT. The reaction mixture was acidified to pH = 2 with conc. HCl, then was extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated in vacuo to give the title compound (0.41 g, 1.48 mmol, 34.6 % yield) as a white solid. $[M - H]^+ = 275.4$.

20

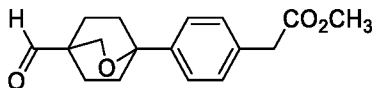
54G. methyl 2-(4-(4-(hydroxymethyl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)acetate



A mixture of compound 54F (410 mg, 1.48 mmol) and TMSCHN₂ (1.48 mL of a 2.0 M solution in hexane; 2.97 mmol) in MeOH (10 mL)/THF (10 mL) was stirred at RT for 2 h, then was concentrated in vacuo. The crude product (oil) was chromatographed (4 g SiO₂; continuous gradient from 0% to 50% EtOAc/hexane over 10 min) to give the title compound (280 mg, 0.964 mmol, 65.0 % yield) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 7.37 (d, *J*=8.3 Hz, 2H), 7.23 (d, *J*=8.3 Hz, 2H), 3.94 (t, *J*=1.4 Hz, 2H), 3.68 (s, 3H), 3.60 (s, 2H), 3.39 (s, 2H), 2.08 - 2.02 (m, 4H), 1.82 - 1.59 (m, 5H).

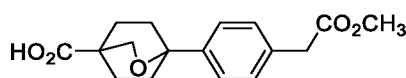
30

54H. methyl 2-(4-(4-formyl-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)acetate



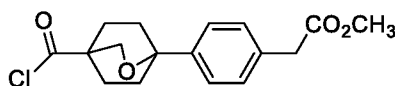
DMSO (0.205 mL, 2.89 mmol) was added dropwise to a solution of (COCl)₂ (0.127 mL, 1.45 mmol) in DCM (5 mL) at -78°C. After stirring at -78°C for 15 min, a solution of compound 54G (280 mg, 0.964 mmol) in DCM (5 mL) was added dropwise and the reaction was stirred at -78°C for 15 min. Et₃N (0.67 mL, 4.82 mmol) was added dropwise and the reaction was allowed to warm to RT over 2 h, then was concentrated in vacuo. The residue was dissolved in EtOAc (5 mL) and washed with 1N aq. HCl (1 x 5 mL), water (2 x 5 mL), satd aq. NaHCO₃, and brine. The organic layer was dried (Na₂SO₄) and concentrated in vacuo to give the crude title compound (278 mg, 0.964 mmol, 100 % yield) as a clear yellowish oil, which was used in the next reaction without further purification. [M + H]⁺ = 289.3.

54I. 1-(4-(2-methoxy-2-oxoethyl)phenyl)-2-oxabicyclo[2.2.2]octane-4-carboxylic acid



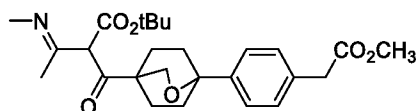
To a mixture of compound 54H (278 mg, 0.964 mmol), 2-methyl-2-butene (7.23 mL of a 2.0M solution in THF; 14.5 mmol), NaH₂PO₄ (578 mg, 4.82 mmol), water (1 mL), and t-BuOH (4 mL) was added NaClO₂ (545 mg, 4.82 mmol) at 0 °C. The reaction mixture was allowed to warm to RT and stirred at RT for 18 h, then was poured into brine and extracted with EtOAc (3X). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (293 mg, 0.963 mmol, 100 % yield) as a white solid. [M - H]⁺ = 303.3; ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, J=8.3 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 4.19 (s, 2H), 3.69 (s, 3H), 3.61 (s, 2H), 2.18 - 2.04 (m, 8H).

54J. Methyl 2-(4-(4-(chlorocarbonyl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)acetate



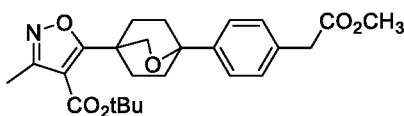
A solution of compound 54I (293 mg, 0.963 mmol) and 1-chloro-N,N,2-trimethylprop-1-en-1-amine (0.127 mL, 0.963 mmol) in DCM (5 mL) was stirred at RT for 1 h, then was concentrated in vacuo to give the crude title compound as an oil (311 mg, 0.96 mmol, 100 % yield). This material was used directly in the next reaction without further purification.

54K. (E)-tert-butyl 2-(1-(4-(2-methoxy-2-oxoethyl)phenyl)-2-oxabicyclo[2.2.2]octane-4-carbonyl)-3-(methylimino)butanoate



To a 0°C solution of (E)-tert-butyl 3-(methylimino)butanoate (247 mg, 1.45 mmol) and pyridine (0.31 mL, 3.85 mmol) in THF (5 mL) was added dropwise a solution of compound 54J (311 mg, 0.96 mmol) in DCM over 10 min. The reaction was stirred at RT for 24 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and water (10 mL each). The aqueous phase was extracted with EtOAc, and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The crude product (oil) was chromatographed (4 g SiO₂; continuous gradient from 0% to 50% EtOAc/hexane over 10 min) to give the title compound (240 mg, 0.53 mmol, 54.4 % yield) as an orange oil. [M + H]⁺ = 458.3.

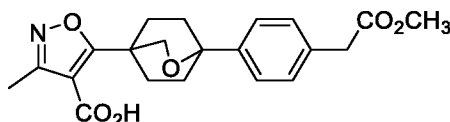
54L. tert-butyl 5-(1-(4-(2-methoxy-2-oxoethyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)-3-methylisoxazole-4-carboxylate



A mixture of compound 54K (240 mg, 0.53 mmol) and NH₂OH.HCl (109 mg, 1.57 mmol) in MeOH (2 mL)/H₂O (0.2 mL) was stirred at 60 °C for 18 h, then was cooled to RT and concentrated in vacuo. The crude product was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min + 2 min hold time

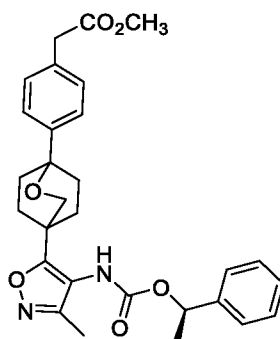
at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (70 mg, 0.16 mmol, 30.2 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, *J*=8.5 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 4.41 (s, 2H), 3.69 (s, 3H), 3.62 (s, 2H), 2.43 - 2.31 (m, 7H), 2.21 - 2.12 (m, 4H), 1.60 (s, 9H); ¹³C NMR (126MHz, CDCl₃) δ 177.9, 172.0, 161.4, 160.6, 144.7, 132.4, 128.9, 124.9, 110.6, 82.3, 72.1, 69.5, 51.9, 40.7, 35.8, 32.7, 28.2, 27.4, 12.3

54M. 5-(1-(4-(2-methoxy-2-oxoethyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)-3-methylisoxazole-4-carboxylic acid



A mixture of compound 54L (70 mg, 0.159 mmol) and formic acid (608 μ L; 15.9 mmol) was stirred at RT for 6 h, then was concentrated in vacuo. The residue was dissolved in EtOAc (2 mL), washed with water, dried (MgSO_4) and concentrated in vacuo to give the title compound (60 mg, 0.156 mmol, 98 % yield) as a white solid. $[\text{M} + \text{H}]^+ = 386.2$

54N. (R)-methyl 2-(4-(4-(3-methyl-4-(((1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)acetate



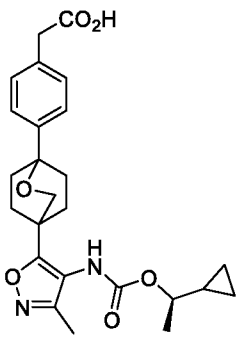
A mixture of compound 54M (18 mg, 0.047 mmol), (PhO₂)PON₃ (0.012 mL, 0.056 mmol), (R)-(+)-1-phenylethanol (10.4 μL, 0.093 mmol), and Et₃N (0.020 mL, 0.140 mmol) in toluene (1 mL) was stirred at 80 °C for 1 h, then was cooled to RT and concentrated in vacuo. The crude oil was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% B to 100% B over 10 min + 2 min hold time at 100% B,

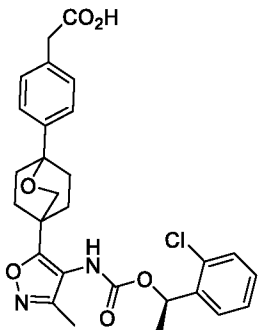
where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (11 mg, 0.022 mmol, 46.7 % yield) as a clear oil.

Example 54

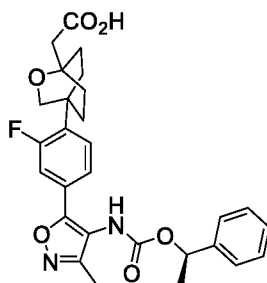
5 A mixture of compound 54N (11 mg, 0.022 mmol) and 2.0 M aq. LiOH (0.109 mL, 0.218 mmol) in THF (1 mL)/MeOH (0.1 mL) was stirred at RT for 2 h, then was acidified to pH = 2 with 1N aq. HCl. The mixture was extracted with EtOAc (2 X 2 mL). The combined organic extracts were washed with water (2 mL) and concentrated in vacuo. The crude product (oil) was purified by preparative HPLC (Phenomenex Axia 5u
10 C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (4.2 mg, 8.39 μmol, 38.5 % yield) as a white solid. [M - H]⁺ = 489.2; ¹H NMR (500 MHz, CDCl₃) δ 7.45 - 7.07 (m, 9H), 5.99 - 5.82 (m, 1H), 4.22 (br. s., 2H), 3.66 (s, 2H), 2.27 - 1.94 (m, 11H), 1.69 - 1.48 (m, 3H); hLPA₁ IC₅₀ = 88 nM.

The following compounds were prepared by the same synthetic sequence as described for the synthesis of Example 54.

Ex #	Structure & Name	Analytical & Biological Data
55	 (R)-2-(4-(4-(4-(((1-cyclopropylethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-2-oxabicyclo [2.2.2] octan-1-yl)phenyl)acetic acid	[M - H]⁺ = 453.3; ¹H NMR (400 MHz, CDCl₃) δ 7.50 (br. s., 1H), 7.35 (d, J=7.5 Hz, 2H), 7.30 - 7.24 (m, 2H), 4.34 - 4.21 (m, 3H), 3.63 (s, 2H), 2.33 - 1.93 (m, 11H), 1.40 - 1.24 (m, 3H), 1.08 - 0.83 (m, 1H), 0.62 - 0.18 (m, 4H); hLPA₁ Binding K_i = 724 nM.

56	 (R)-2-(4-(4-(4-(((1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)acetic acid	$[M + H]^+ = 525.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 - 7.08 (m, 8H), 6.33 - 6.13 (m, 1H), 5.79 (br. s., 1H), 4.23 (s, 2H), 3.63 (s, 2H), 2.31 - 1.93 (m, 11H), 1.69 - 1.47 (m, 3H); hLPA₁ IC₅₀ = 93 nM.
----	---	--

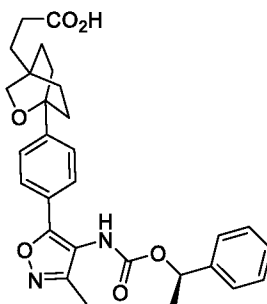
Example 57. 2-(4-(2-fluoro-4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid



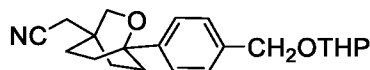
5 Example 57 was prepared according to the general procedures described for the synthesis of Example 1 by using Intermediate 2 instead of Intermediate 1. LCMS $[M + H]^+ = 509.0$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 - 7.27 (m, 6H), 7.17 (t, $J=8.0$ Hz, 2H), 6.09 - 5.93 (m, 1H), 5.87 (q, $J=6.6$ Hz, 1H), 4.25 (s, 2H), 2.56 (s, 3H), 2.27 - 2.21 (m, 2H), 2.20 - 1.80 (m, 8H), 1.62 (br. s., 3H); hLPA₁ IC₅₀ = 41 nM.

10

Example 58. 3-(1-(4-(3-methyl-4-(((R)-1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)propanoic acid

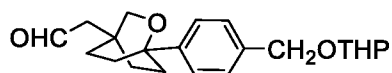


58A. 2-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl) acetonitrile



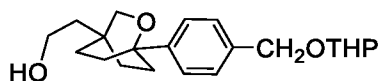
A mixture of compound 54A (1 g, 2.055 mmol) and NaCN (0.302 g, 6.16 mmol) in DMSO (5 mL) was stirred at 80 °C for 3 days, then was cooled to RT and partitioned between EtOAc and water (20 mL each). The organic layer was washed with water, dried (MgSO₄), and concentrated in vacuo. The crude oil was chromatographed (12 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (0.65 g, 1.904 mmol, 93 % yield) as clear oil. [M - OTHP]⁺ = 240.1; ¹H NMR (400 MHz, CDCl₃) δ: 7.37 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.77 (d, J = 12.0 Hz, 1H), 4.71 - 4.68 (m, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.99 - 3.88 (m, 3H), 3.59 - 3.51 (m, 1H), 2.23 (s, 2H), 2.10 (t, J = 8.2 Hz, 4H), 1.93 --1.49 (m, 10H).

58B. 2-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl) acetaldehyde



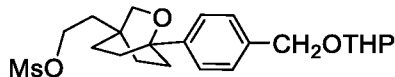
A solution of 1M DIBALH in CH₂Cl₂ (2.28 mL, 2.28 mmol) was added dropwise to a solution of compound 58A (0.65 g, 1.90 mmol) in CH₂Cl₂ (10 mL) at -78 °C under N₂. The reaction mixture was stirred at -78 °C for 2 h, then Celite (1 g) was added and the reaction was quenched with satd aq. NH₄Cl (2 mL). The mixture was stirred at RT for 30 min, then MgSO₄ (1 g) was added and the mixture was stirred at RT for 30 min, then was filtered. The solids were washed with CH₂Cl₂ (3x). The combined filtrates were concentrated in vacuo. The crude oil was chromatographed (12 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (0.58 g, 1.684 mmol, 88 % yield) as a clear oil. ¹H NMR (CDCl₃) δ 9.85 (t, J = 2.7 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.35 - 7.30 (m, 2H), 4.77 (dd, J = 12.0, 2.1 Hz, 1H), 4.69 (t, J = 3.5 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.01 - 3.88 (m, 3H), 3.60 - 3.49 (m, 1H), 2.28 (d, J = 2.8 Hz, 2H), 2.12 - 2.03 (m, 4H), 1.96 - 1.47 (m, 10H).

58C. 2-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl) ethanol



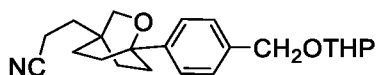
A solution of 1.0 M DIBALH in CH₂Cl₂ (2.02 mL, 2.021 mmol) was added dropwise to a solution of compound 58B (0.58 g, 1.684 mmol) in CH₂Cl₂ (10 ml) at -78 °C under N₂. The reaction mixture was stirred at -78 °C for 2 h, after which Celite (1 g) was added and the reaction was quenched with satd aq. NH₄Cl (2 mL). The reaction was stirred at RT for 30 min, MgSO₄ (1 g) was added and the mixture was stirred at RT for 30 min, then was filtered. The solids were washed with CH₂Cl₂ (3x). The combined filtrates were concentrated in vacuo. The crude oil was chromatographed (12 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (0.49 g, 1.414 mmol, 84 % yield) as a clear oil. ¹H NMR (CDCl₃) δ 7.38 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.77 (d, J = 11.9 Hz, 1H), 4.69 (t, J = 3.6 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 3.98 - 3.84 (m, 3H), 3.72 (t, J = 7.3 Hz, 2H), 3.60 - 3.50 (m, 1H), 2.09 - 1.98 (m, 4H), 1.93 - 1.80 (m, 1H), 1.79 - 1.44 (m, 12H).

58D. 2-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl) ethyl methanesulfonate



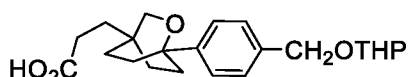
MsCl (0.132 mL, 1.70 mmol) was added dropwise at RT to a solution of compound 58C (0.49 g, 1.41 mmol) and TEA (0.30 mL, 2.12 mmol) in CH₂Cl₂ (5 mL). The reaction was stirred at RT for 2 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and water. The organic layer was washed with 1N aq. HCl and water, dried (MgSO₄), and concentrated in vacuo to give the title compound (0.6 g, 1.413 mmol, 100 % yield) as a light yellowish oil which was used directly in the next reaction without further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.39 - 7.35 (m, 2H), 7.34 - 7.29 (m, 2H), 4.76 (d, J=11.8 Hz, 1H), 4.69 (t, J=3.6 Hz, 1H), 4.48 (d, J=11.8 Hz, 1H), 4.29 (t, J=7.0 Hz, 2H), 3.92 (ddd, J=11.3, 8.5, 3.0 Hz, 1H), 3.88 (s, 2H), 3.57 - 3.51 (m, 1H), 3.02 (s, 3H), 2.08 - 2.02 (m, 4H), 1.92 - 1.82 (m, 1H), 1.80 - 1.49 (m, 11H).

58E. 3-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl) propanenitrile



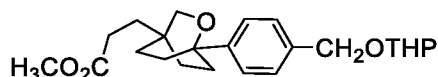
A mixture of compound 58D (0.60 g, 1.41 mmol) and NaCN (0.14 g, 2.83 mmol) in DMSO (5 mL) was stirred at 50 °C for 18 h, then was cooled to RT and partitioned between EtOAc and water. The organic layer was washed with water, dried (MgSO₄), and concentrated in vacuo. The crude oil was chromatographed (24 g SiO₂; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (0.4 g, 1.125 mmol, 80 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.40 - 7.36 (m, 2H), 7.35 - 7.31 (m, 2H), 4.78 (d, *J*=12.1 Hz, 1H), 4.70 (t, *J*=3.6 Hz, 1H), 4.49 (d, *J*=11.8 Hz, 1H), 3.93 (ddd, *J*=11.3, 8.4, 3.2 Hz, 1H), 3.84 (s, 2H), 3.58 - 3.52 (m, 1H), 2.34 - 2.28 (m, 2H), 2.06 (t, *J*=8.0 Hz, 4H), 1.91 - 1.83 (m, 1H), 1.78 - 1.50 (m, 11H).

58F. 3-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl) propanoic acid



A mixture of compound 58E (200 mg, 0.563 mmol) and 40% aq. KOH (1.13 mL, 11.3 mmol) in ethylene glycol (5 mL) was stirred at 160 °C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc and 1N aq. HCl. The organic layer was washed with water, dried (MgSO₄), and concentrated in vacuo to give the title compound (200 mg, 0.534 mmol, 95 % yield) as a white solid. [M - H]⁺ = 373.3; ¹H NMR (500 MHz, CDCl₃) δ 7.31 - 7.27 (m, 2H), 7.25 - 7.21 (m, 2H), 4.68 (d, *J*=12.1 Hz, 1H), 4.62 (t, *J*=3.6 Hz, 1H), 4.40 (d, *J*=12.1 Hz, 1H), 3.85 (ddd, *J*=11.3, 8.5, 3.0 Hz, 1H), 3.76 (s, 2H), 3.51 - 3.44 (m, 1H), 2.28 - 2.22 (m, 2H), 1.96 (t, *J*=7.8 Hz, 4H), 1.84 - 1.73 (m, 1H), 1.70 - 1.41 (m, 11H).

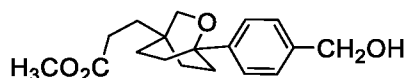
58G. Methyl 3-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-oxabicyclo[2.2.2] octan-4-yl)propanoate



A solution of 2 M TMSCHN₂ in hexane (0.80 mL, 1.602 mmol) was added to a solution of compound 58F (200 mg, 0.534 mmol) in THF (5 mL) and MeOH (1 mL). The reaction was stirred at RT for 2 h, then was concentrated in vacuo to give the title

compound (200 mg, 0.515 mmol, 96 % yield) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.40 - 7.35 (m, 2H), 7.34 - 7.29 (m, 2H), 4.77 (d, $J=11.8$ Hz, 1H), 4.69 (t, $J=3.6$ Hz, 1H), 4.48 (d, $J=12.1$ Hz, 1H), 3.93 (ddd, $J=11.3, 8.5, 3.0$ Hz, 1H), 3.83 (s, 2H), 3.69 (s, 3H), 3.58 - 3.51 (m, 1H), 2.33 - 2.26 (m, 2H), 2.03 (t, $J=8.0$ Hz, 4H), 1.87 (d, $J=9.4$ Hz, 1H), 1.78 - 1.50 (m, 11H).

58H. Methyl 3-(1-(4-(hydroxymethyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)propanoate



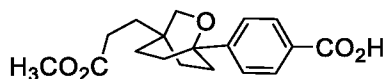
A mixture of compound 58G (200 mg, 0.515 mmol) and PPTS (13 mg, 0.051 mmol) in MeOH (10 mL) was stirred at 50 °C for 3 h, then was cooled to RT and concentrated in vacuo. The crude oil was chromatographed (12 g SiO_2 ; continuous gradient from 0% to 50% EtOAc in hexane over 10 min) to give the title compound (156 mg, 0.513 mmol, 100 % yield) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.42 - 7.36 (m, 2H), 7.34 - 7.28 (m, 2H), 4.66 (s, 2H), 3.83 (s, 2H), 3.69 (s, 3H), 2.33 - 2.26 (m, 2H), 2.03 (t, $J=8.1$ Hz, 4H), 1.76 - 1.60 (m, 5H), 1.58 - 1.50 (m, 2H).

58I. methyl 3-(1-(4-formylphenyl)-2-oxabicyclo[2.2.2]octan-4-yl)propanoate



A mixture of compound 58H (128 mg, 0.421 mmol), Dess-Martin periodinane (268 mg, 0.631 mmol), and Na_2CO_3 (446 mg, 4.21 mmol) in CH_2Cl_2 (5 mL) was stirred at RT for 3 h, then was filtered. The filtrate was concentrated in vacuo. The residue was dissolved in EtOAc and washed with 1N aq. NaOH and water, dried (MgSO_4), and concentrated in vacuo to give the title compound (126 mg, 0.417 mmol, 99 % yield) as a white solid, which was used in the next reaction without further purification. $[\text{M} + \text{H}]^+ = 303.2$.

58J. 4-(4-(3-methoxy-3-oxopropyl)-2-oxabicyclo[2.2.2]octan-1-yl)benzoic acid



To a 0 °C mixture of compound 58I (127 mg, 0.420 mmol), a 2M solution of 2-methyl-2-butene in THF (3.15 mL, 6.30 mmol) and NaH_2PO_4 (252 mg, 2.100 mmol) in

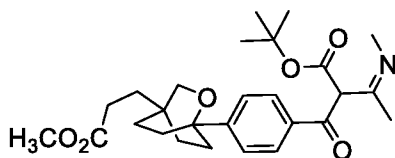
water (1 mL) and t-BuOH (4 mL) was added NaClO₂ (190 mg, 2.100 mmol). The reaction mixture was allowed to warm to RT and stirred at RT for 18 h, then was poured into brine and extracted with EtOAc (5 mL x 3). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude oil was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (110 mg, 0.346 mmol, 82 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.07 (d, *J*=8.5 Hz, 2H), 7.51 (d, *J*=8.5 Hz, 2H), 3.86 (s, 2H), 3.71 (s, 3H), 2.36 - 2.28 (m, 2H), 2.14 - 1.99 (m, 4H), 1.78 - 1.63 (m, 4H), 1.58 (t, *J*=8.4 Hz, 2H).

58K. methyl 3-(1-(4-(chlorocarbonyl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)propanoate



A mixture of compound 58J (110 mg, 0.346 mmol) and 1-chloro-N,N,2-trimethyl prop-1-en-1-amine (0.055 mL, 0.415 mmol) in CH₂Cl₂ (1 mL) was stirred at RT for 1 h. Analytical HPLC showed that the reaction was complete. This crude product was used in the next reaction directly.

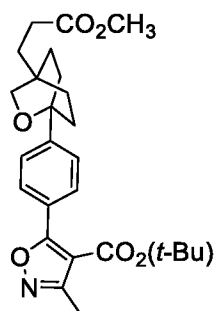
58L. (E)-tert-butyl 2-(4-(4-(3-methoxy-3-oxopropyl)-2-oxabicyclo[2.2.2]octan-1-yl)benzoyl)-3-(methylimino)butanoate



A solution of compound 58K (116 mg, 0.344 mmol) in CH₂Cl₂ (2 mL) was added dropwise to a solution of (E)-tert-butyl 3-(methylimino)butanoate (88 mg, 0.517 mmol) and pyridine (0.111 mL, 1.38 mmol) in THF (1 mL) at 0°C over 5 min. The reaction was allowed to warm to RT and stirred at RT for 24 h, then was concentrated in vacuo and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc, and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give the crude title compound (162 mg, 0.344 mmol, 100 % yield) as an orange

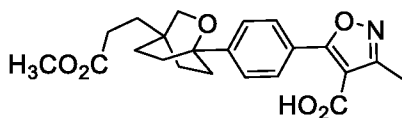
oil. This crude compound was used in the next reaction without further purification. $[M + H]^+ = 472.2$.

58M. tert-butyl 5-(4-(4-(3-methoxy-3-oxopropyl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)-3-methylisoxazole-4-carboxylate



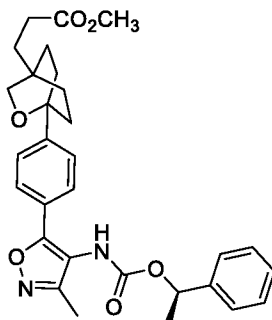
A mixture of crude compound 58L (162 mg, 0.344 mmol) and $\text{NH}_2\text{OH} \cdot \text{HCl}$ (71.6 mg, 1.031 mmol) in MeOH (3 mL)/ H_2O (0.3 mL) was stirred at 60 °C for 18 h. LC-MS showed that the reaction was complete. The mixture was concentrated in vacuo, and the residue was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min + 3 min hold time at 100% B, where A = 90:10:0.1 $\text{H}_2\text{O}:\text{MeOH}:\text{TFA}$ and B = 90:10:0.1 MeOH: $\text{H}_2\text{O}:\text{TFA}$) to give the title compound (87 mg, 0.191 mmol, 55.6 % yield) as white solid. $[M + H]^+ = 456.5$; ^1H NMR (500 MHz, CDCl_3) δ 7.86 - 7.81 (m, 2H), 7.53 - 7.48 (m, 2H), 3.85 (s, 2H), 3.70 (s, 3H), 2.48 (s, 3H), 2.33 - 2.26 (m, 2H), 2.11 - 1.99 (m, 4H), 1.75 - 1.62 (m, 4H), 1.59 - 1.53 (m, 2H), 1.52 (s, 9H).

58N. 5-(4-(4-(3-methoxy-3-oxopropyl)-2-oxabicyclo[2.2.2]octan-1-yl)phenyl)-3-methylisoxazole-4-carboxylic acid



A mixture of compound 58M (87 mg, 0.191 mmol) and HCO_2H (146 μL , 3.82 mmol) was stirred at RT for 2 h, then was concentrated in vacuo to give the title compound (75 mg, 0.188 mmol, 98 % yield) as a white solid. $[M - H]^+ = 398.3$.

58O. (R)-methyl-3-(1-(4-(3-methyl-4-(((1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-4-yl)propanoate

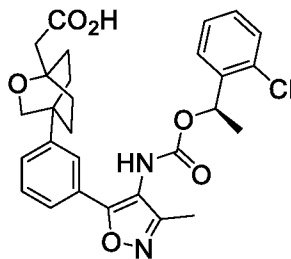


A mixture of compound 58N (21.7 mg, 0.054 mmol), (R)-(+)-1-phenylethanol (13.3 mg, 0.109 mmol), (PhO)₂PON₃ (18 mg, 0.065 mmol), and TEA (0.030 mL, 0.217 mmol) in toluene (1 mL) was stirred at 80 °C for 1 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (27 mg, 0.052 mmol, 96 % yield) as a clear oil. [M + H]⁺ = 519.4; ¹H NMR (400 MHz, CDCl₃) δ 7.48 - 7.21 (m, 7H), 7.19 - 7.09 (m, 2H), 6.29 - 5.77 (m, 1H), 3.85 (s, 2H), 3.70 (s, 3H), 2.40 - 2.13 (m, 4H), 2.09 - 1.92 (m, 4H), 1.75 - 1.33 (m, 9H).

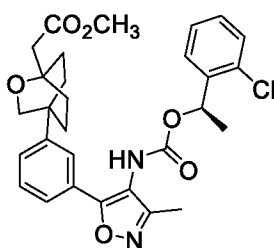
Example 58

A mixture of compound 58O (27 mg, 0.052 mmol) and 2.0 M aq. LiOH (0.2 mL, 0.40 mmol) in THF (1 mL)/MeOH (0.1 mL) was stirred at RT for 2 h, then was acidified to pH = 2 with 1N aq. HCl. The mixture was extracted with EtOAc (2X). The combined organic extracts were washed with water and concentrated in vacuo. The crude oil was purified by preparative HPLC (Phenomenex Axia 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (12.5 mg, 0.024 mmol, 46.6 % yield) as a white solid. [M - H]⁺ = 503.2; ¹H NMR (500 MHz, CDCl₃) δ 8.64 (br. s., 1H), 7.84 - 6.70 (m, 9H), 6.27 - 5.78 (m, 1H), 3.86 (s, 2H), 2.42 - 2.30 (m, 2H), 2.21 (br. s., 3H), 2.04 (t, J=8.0 Hz, 4H), 1.78 - 1.33 (m, 9H); hLPA₁ IC₅₀ = 157 nM.

Example 59. 2-(4-(3-(4-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetic acid



5 59A. methyl 2-(4-(3-(4-(((R)-1-(2-chlorophenyl)ethoxy)carbonyl)amino)-3-methylisoxazol-5-yl)phenyl)-2-oxabicyclo[2.2.2]octan-1-yl)acetate



A solution of Intermediate 19 (17 mg, 0.044 mmol), intermediate 6 (15.8 mg, 0.044 mmol), K₂CO₃ (18.2 mg, 0.13 mmol) and PdCl₂(dppf) (3.2 mg, 0.0044 mmol) in THF (4 mL) and water (1 mL) was purged with Ar for 5 min. The reaction mixture was then heated to 80 °C for 18 h under Ar, then was cooled to RT and filtered through Celite. The filtrate was partitioned between EtOAc (3 mL) and water (3 mL); the aqueous phase was extracted with EtOAc (2x3 mL). The combined organic extracts were washed with water (2 mL), brine (2 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was chromatographed (SiO₂ ISCO column; continuous gradient from 0% to 100% EtOAc in hexanes over 20 min) to give the title compound as a colorless oil. (4.5 mg, 0.0084 mmol, 19% yield) LCMS [M + H]⁺ = 539.2; ¹H NMR (CDCl₃) δ: 7.70-7.76 (m, 1H), 7.58-7.68 (m, 1H), 7.48-7.55 (m, 1H), 7.33-7.45 (m, 4H), 6.26 (br d, J=6.6 Hz, 1H), 4.00-4.06 (m, 2H), 3.73 (s, 3H), 2.51 (s, 2H), 2.29 (s, 3H), 2.08-2.16 (m, 4H), 1.88-1.95 (m, 4H), 1.62-1.70 (m, 2H), 1.27-1.32 (m, 2H).

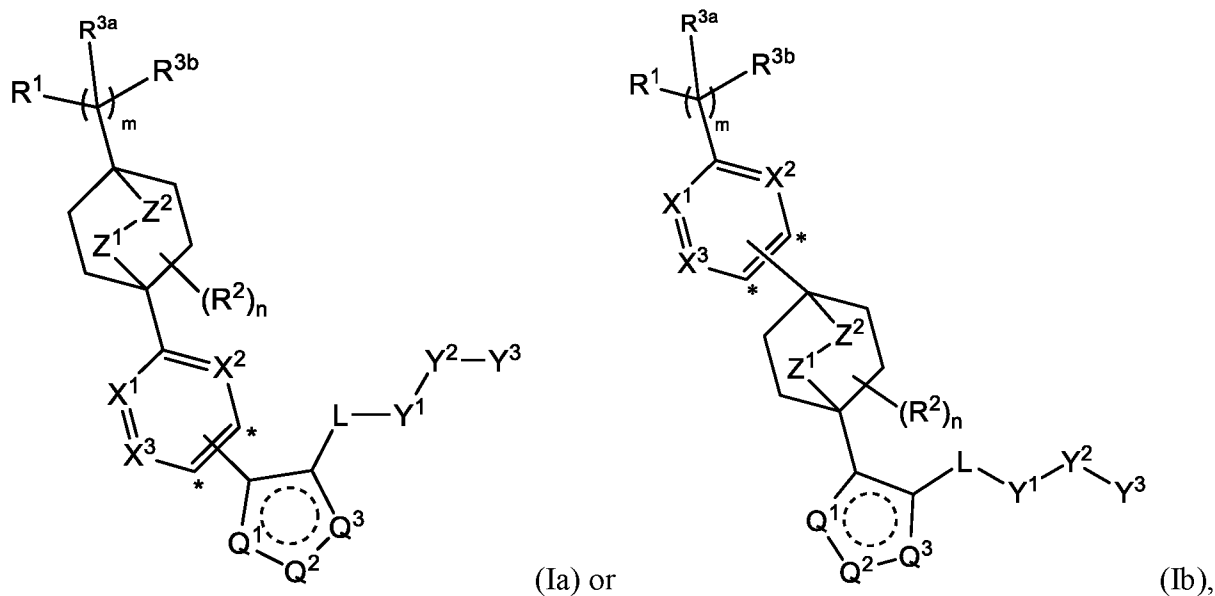
Example 59

To a solution of compound 59A (4.5 mg, 8.35 μmol) in THF (1 mL) was added 2M aq. LiOH (0.04 mL, 0.08 mmol). The reaction was stirred at RT for 18 h, then was concentrated *in vacuo*. The residue was dissolved in H₂O (1 mL), and the pH was

adjusted with 1N aq. HCl to ~3 and extracted with EtOAc (2 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by preparative LC/MS: Column: Waters XBridge C18, 19 x 200 mm, 5-μm particles; Guard Column: Waters XBridge C18, 19 x 10 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: 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 concentrated *in vacuo* by centrifugal evaporation to give the title compound (2.2 mg, 0.004mmol, 47.7% yield). LCMS [M + H]⁺=525.3; ¹H NMR (DMSO-d₆) δ: 9.41 (br s, 1H), 7.72 (br s, 1H), 7.55-7.65 (m, 2H), 7.42-7.52 (m, 4H), 7.38 (br d, J=7.6 Hz, 1H), 5.77-6.20 (m, 1H), 3.90 (br s, 2H), 3.46 (br s, 2H), 2.34 (s, 2H), 2.14 (br s, 3H), 2.00 (br s, 4H), 1.87 (br s, 4H), 1.55 (br d, J=5.8 Hz, 2H); hLPA₁ Antagonist IC₅₀ = 95 nM.

What is claimed is:

1. A compound of Formula (Ia) or (Ib):

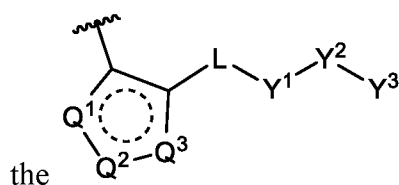


or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof,
wherein:

one of Z^1 and Z^2 is O, and the other one is CH_2 ;

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

Q^1 , Q^2 , and Q^3 are independently N, O, NR^{5a} , or CR^{5b} , and the dashed circle denotes bonds forming an aromatic ring; provided that at least one of Q^1 , Q^2 , and Q^3 is not CR^{5b} ;

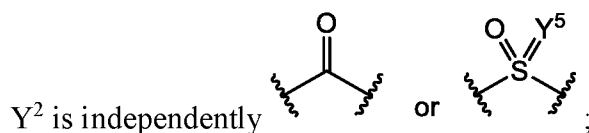


moiety is attached to one of the two asterisked (*)

positions in Formula (Ia) or (Ib);

L is independently a covalent bond or C_{1-4} alkylene substituted with 0 to 4 R^9 ;

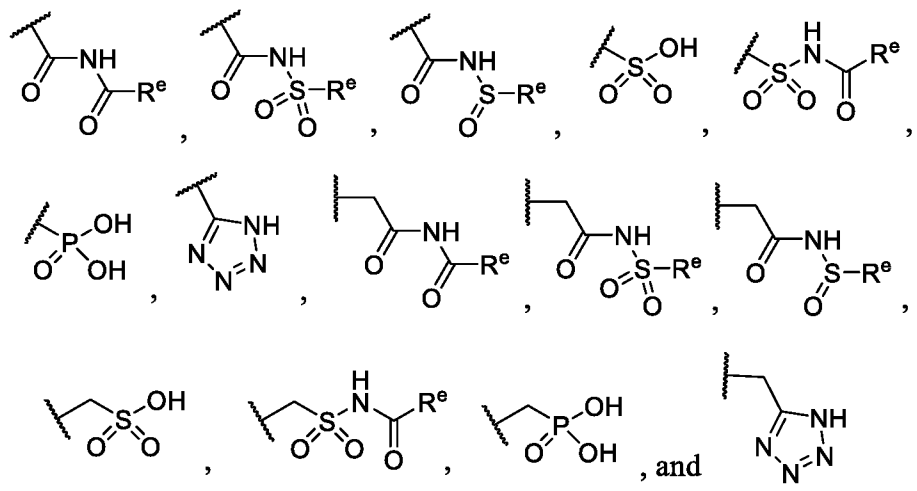
Y^1 is independently O or NR^7 ;



Y^3 is independently OR^4 or NR^8R^4 , with the proviso that when Y^1 is O, then Y^3 is not OR^4 ;

Y^5 independently is O or NH;

R^1 is independently cyano, $-C(O)OR^{11}$, $-C(O)NR^{12a}R^{12b}$,



R^2 is each independently halo, cyano, hydroxyl, amino, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} alkylamino, $-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl), $-(CH_2)_{0-1}$ -phenyl, or C_{1-6} alkyl substituted with 0 to 3 R^c ;

R^{3a} is independently hydrogen, halo, hydroxyl, or C_{1-4} alkyl;

R^{3b} is independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or C_{1-6} alkyl substituted with 0 to 2 R^a ;

or alternatively, R^{3a} and R^{3b} together, with the carbon atom they are attached to, form a C_{3-4} carbocyclyl;

R^4 is $-L_1-R^{4a}$;

L_1 is independently a covalent bond or C_{1-4} alkylene substituted with 0 to 4 R^9 ;

R^{4a} is independently C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkenyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3 to 8-membered heterocyclyl, 5 to 6-membered heteroaryl; wherein each of the alkyl, alkenyl, alkylene, cycloalkyl, aryl, heterocyclyl, and heteroaryl, by itself or as part of other moiety, is independently substituted with 0 to 3 R^{10} ;

R^{5a} is independently hydrogen, C_{1-4} haloalkyl, $-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl), $-(CH_2)_{0-1}$ -phenyl, or C_{1-6} alkyl substituted with 0 to 3 R^a ;

R^{5b} is independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} alkylamino, $-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl), $-(CH_2)_{0-1}$ -phenyl, or C_{1-6} alkyl substituted with 0 to 3 R^b ;

R^6 is each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-4} alkylamino, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or C_{1-6} alkyl substituted with 0 to 1 R^b ;

R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl or C_{1-6} alkyl substituted with 0 to 1 R^c ;

R^9 is each independently halo, oxo, cyano, hydroxyl, amino, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, or C_{1-6} alkyl substituted with 0 to 3 R^a ;

R^{10} is each independently halo, hydroxyl, amino, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, phenyl, or 5 to 6 membered heteroaryl, C_{1-6} alkyl substituted with 0 to 3 R^b ;

R^{11} , R^{12a} and R^{12b} are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or benzyl;

R^a is independently halo, cyano, hydroxyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

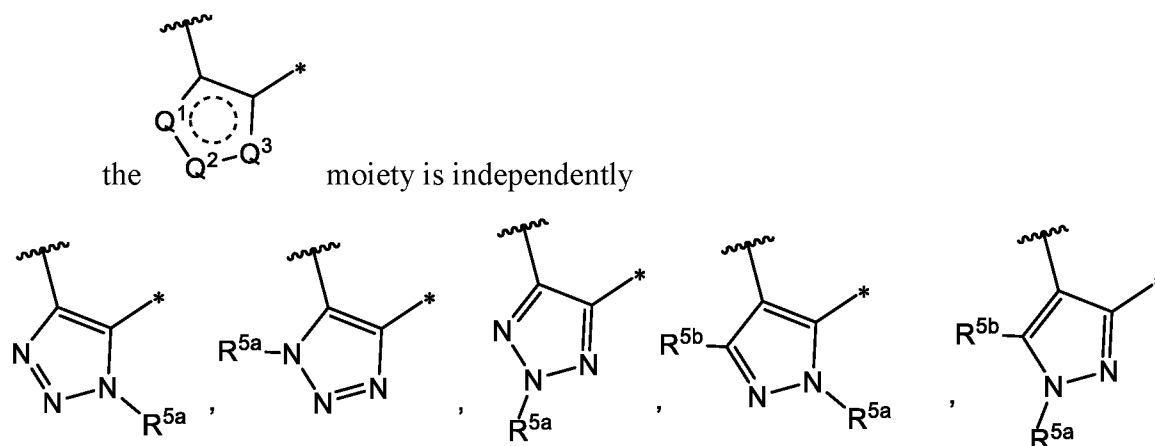
R^b is independently halo, cyano, hydroxyl, amino, C_{1-4} alkoxy, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

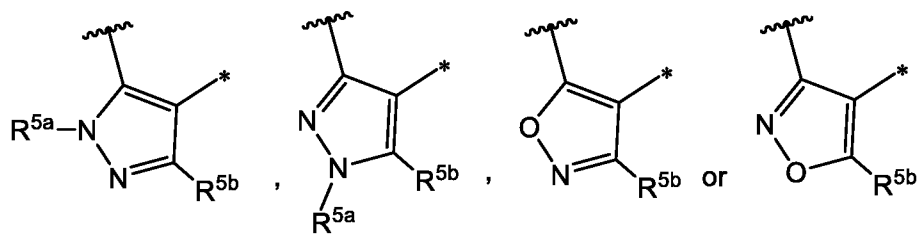
R^c is independently C_{1-4} haloalkyl, C_{3-6} cycloalkyl, or C_{1-6} alkyl substituted with 0 to 3 R^a ;

m is an integer of 0, 1, or 2; and

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

2. The compound according to claim 1, wherein:



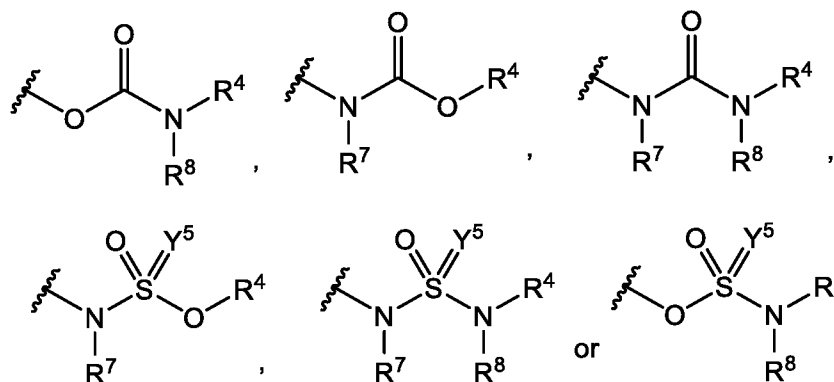


* denotes the attachment point to L; and

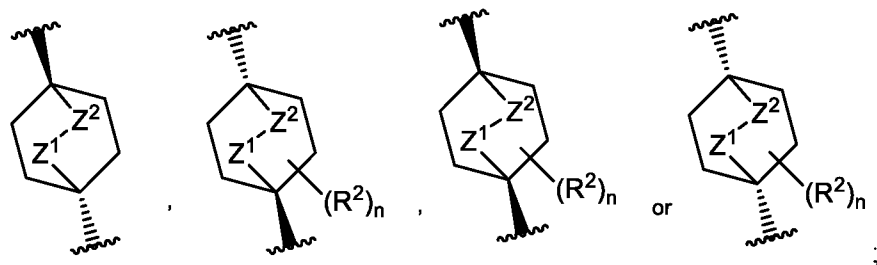
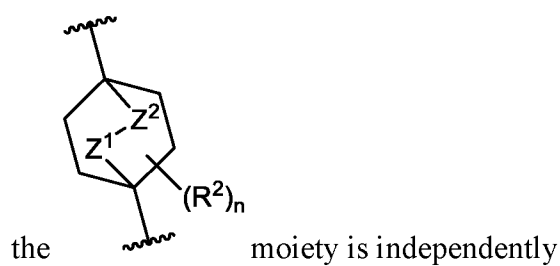
R^{5a} and R^{5b} are the same as defined in Claim 1.

3. The compound according to claim 1 or 2, wherein:

the $\text{---Y}^1\text{---Y}^2\text{---Y}^3$ moiety is independently

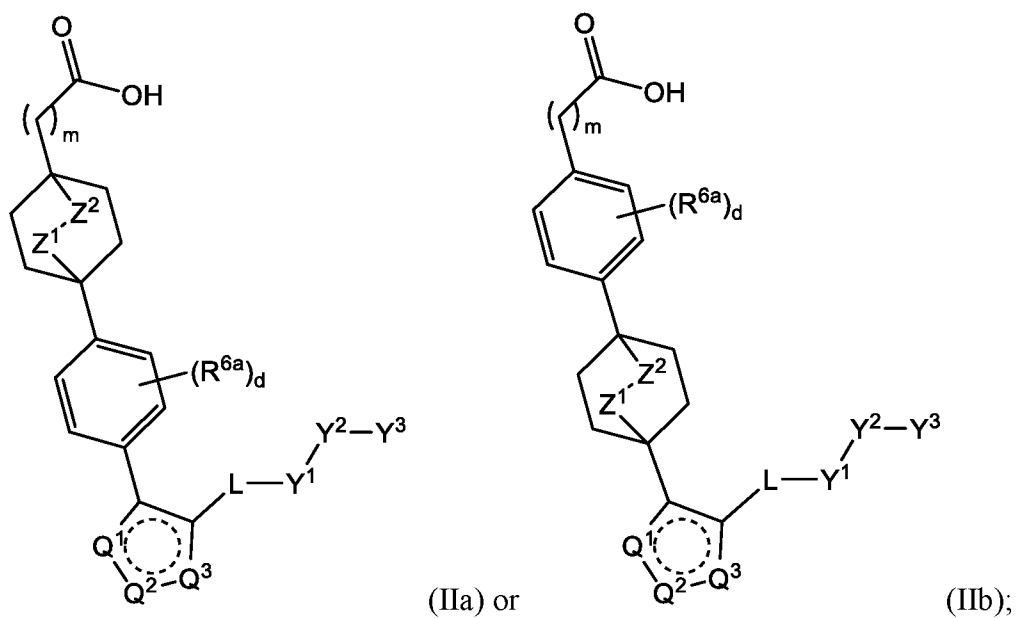


4. The compound according to any one of claims 1 to 3, wherein L is a covalent bond or C_{1-2} alkylene.
5. The compound according to any one of claims 1 to 4, wherein:
 X^1 , X^2 , and X^3 are independently CH or CR^{6a} ; or one of X^1 , X^2 , and X^3 is N, and the remaining ones are CH or CR^{6a} ; and R^{6a} is independently halo, hydroxyl, C_{1-6} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.
6. The compound according to any one of claims 1 to 5, wherein R^{3a} and R^{3b} are independently hydrogen or C_{1-4} alkyl.
7. The compound according to any one of claims 1 to 6, wherein R^1 is CO_2H .
8. The compound according to any one of claims 1 to 7, wherein:



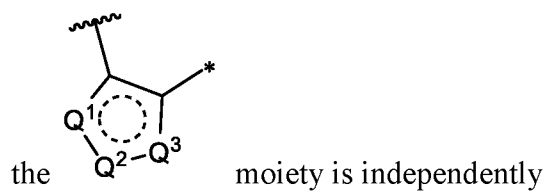
-Z¹-Z²- is -O-CH₂- or -CH₂-O-; and
n is 0.

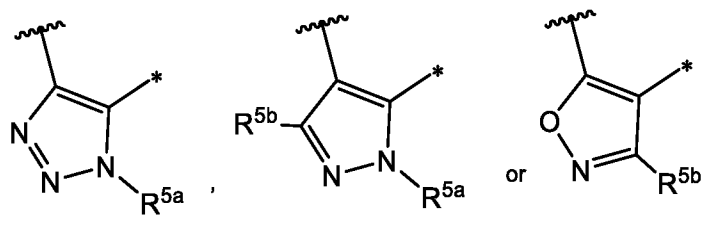
9. A compound of Formula (IIa) or (IIb):



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

$-Z^1-Z^2-$ is $-O-CH_2-$ or $-CH_2-O-$;

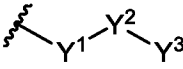


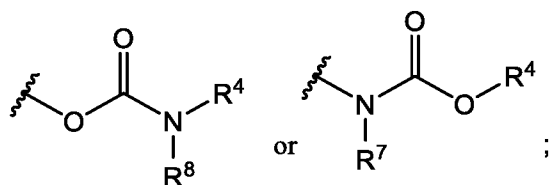


m is an integer of 1 or 2;

* denotes the attachment point to L;

L is independently a covalent bond or -CH₂-;

the  moiety is independently



R⁴ is independently C₃₋₆ cycloalkyl, -(CH₂)-C₃₋₆ cycloalkyl, -(CH(C₁₋₂ alkyl))-C₃₋₆ cycloalkyl, -(CH₂)-phenyl or -(CH(C₁₋₂ alkyl))-phenyl, wherein each of said cycloalkyl and phenyl is independently substituted with 0 to 3 R¹⁰;

R^{5a} is independently C₁₋₆ alkyl, or -CH₂-(C₃₋₆ cycloalkyl);

R^{5b} is independently hydrogen, halo, cyano, hydroxyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, or C₁₋₄ haloalkoxy;

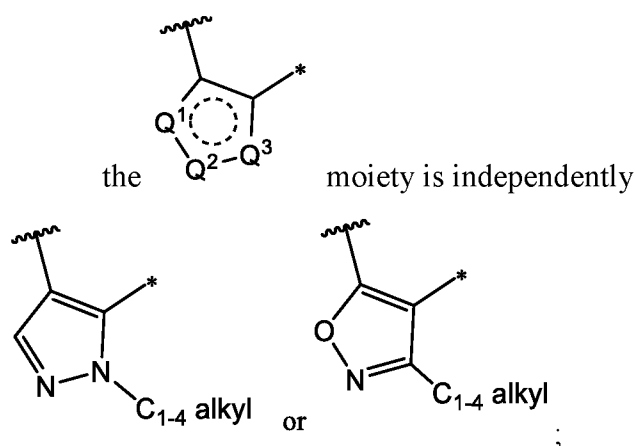
R^{6a} is each independently halo, hydroxyl, C₁₋₆ alkyl, C₁₋₄ haloalkyl, or C₁₋₄ alkoxy;

R⁷ and R⁸ are each independently hydrogen or C₁₋₂ alkyl;

R¹⁰ is each independently halo, cyano, hydroxyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkoxy; and

d is independently 0, 1 or 2.

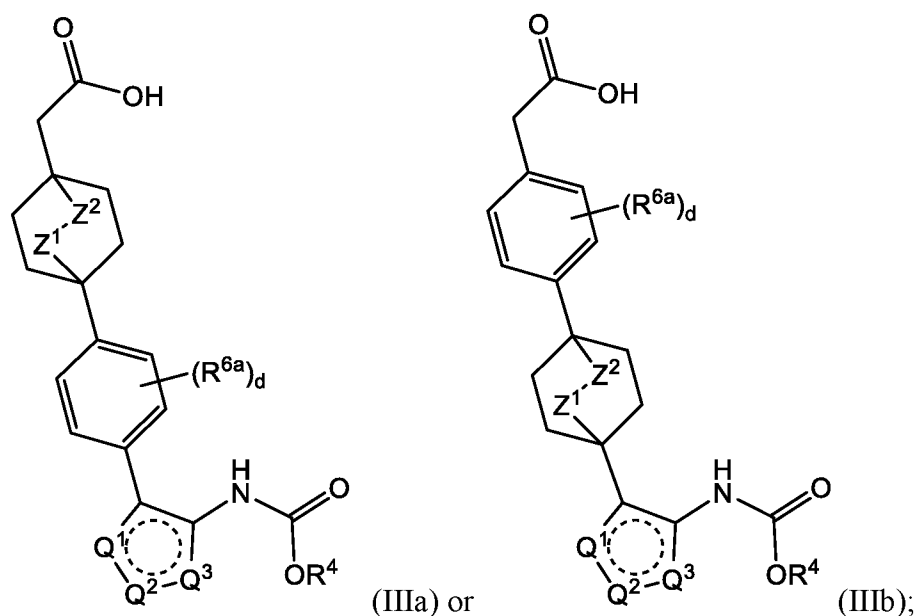
10. The compound according to claim 9, wherein:



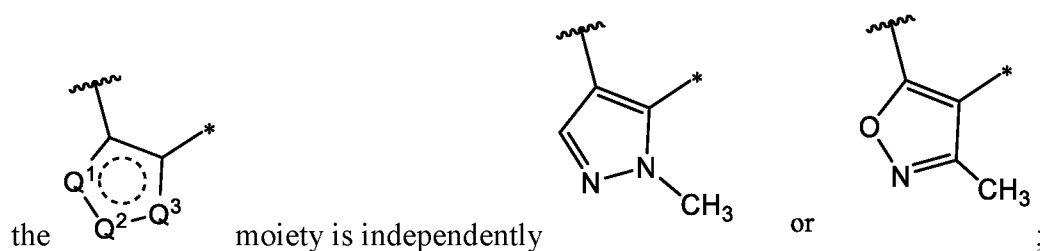
m is an integer of 1; and

R^4 is independently $-(CH_2)-C_{3-6}$ cycloalkyl, $-(CH(C_{1-2} \text{ alkyl}))-C_{3-6}$ cycloalkyl, $-(CH_2)$ -phenyl or $-(CH(C_{1-2} \text{ alkyl}))-phenyl$, wherein each of said cycloalkyl and phenyl is independently substituted with 0 to 2 R^{10} .

11. A compound of Formula (IIIa) or (IIIb):



wherein: $-Z^1-Z^2-$ is $-O-CH_2-$ or $-CH_2-O-$;



* denotes the attachment point to the nitrogen atom of $-NH-C(O)-OR^4$;

R^4 is independently $-(CH_2)$ -phenyl, or $-(CH(CH_3))$ -phenyl, wherein said phenyl is independently substituted with 0 to 2 R^{10} ;

R^{6a} is each independently halo or C_{1-4} alkyl;

R^{10} is each independently halo, cyano, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy; and

d is independently 0 or 1.

12. The compound according to claim 1, which is selected from any one of Examples 1 to 59, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof.
13. A pharmaceutical composition comprising one or more compounds according to any one of claims 1 to 12, or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable carrier or diluent.
14. Use of a compound or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 12, or a pharmaceutical composition according to claim 13, for therapy
15. Use of a compound or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 12, or a pharmaceutical composition according to claim 13, for treating a disease, disorder, or condition associated with dysregulation of lysophosphatidic acid receptor 1 (LPA1).
16. The use according to claim 15, wherein the disease, disorder, or condition is related to pathological fibrosis, transplant rejection, cancer, osteoporosis, or inflammatory disorders.
17. The use according to claim 16, wherein the pathological fibrosis is pulmonary, liver, renal, cardiac, dermal, ocular, or pancreatic fibrosis.

18. The use according to claim 15, 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.
19. The use according to claim 16, 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.
20. Use of a compound or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 12, or a pharmaceutical composition according to claim 13, for treating fibrosis in a mammal comprising administering a therapeutically effective amount of the compound or the pharmaceutical composition, to the mammal in need thereof.
21. The use according to claim 20, wherein the fibrosis is idiopathic pulmonary fibrosis (IPF), nonalcoholic steatohepatitis (NASH), chronic kidney disease, diabetic kidney disease, and systemic sclerosis.
22. Use of a compound or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 12, or a pharmaceutical composition according to claim 13, for 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 the compound or the pharmaceutical composition, to the mammal in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/051272

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D493/08 A61K31/4155 A61K31/42 A61P11/00 A61P19/10 A61P35/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2019/126085 A1 (SQUIBB BRISTOL MYERS CO [US]) 27 June 2019 (2019-06-27) claims 1,24	1-22
A	WO 2014/151247 A1 (SQUIBB BRISTOL MYERS CO [US]) 25 September 2014 (2014-09-25) cited in the application claim 1	1-22
A	WO 2012/078805 A1 (AMIRA PHARMACEUTICALS INC [US]; SQUIBB BRISTOL MYERS CO [US] ET AL.) 14 June 2012 (2012-06-14) paragraph [0018]; claim 1	1-22
A	WO 2017/223016 A1 (BRISTOL-MYERS SQUIBB COMPANY [US]) 28 December 2017 (2017-12-28) claim 1	1-22
	- / - -	
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 28 October 2019		Date of mailing of the international search report 06/11/2019
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Gettins, Marc

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/051272

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/160873 A1 (NOVARTIS AG [CH]; CHEN XIN [US] ET AL.) 31 October 2013 (2013-10-31) cited in the application claims 1,19 -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/051272

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019126085	A1	27-06-2019	NONE
WO 2014151247	A1	25-09-2014	AU 2014235172 A1 05-11-2015 BR 112015021596 A2 18-07-2017 CA 2905448 A1 25-09-2014 CN 105189516 A 23-12-2015 EA 201591805 A1 29-01-2016 EP 2970327 A1 20-01-2016 IL 241323 A 31-10-2018 JP 2016512556 A 28-04-2016 KR 20150128860 A 18-11-2015 MX 362383 B 15-01-2019 SG 11201506799R A 29-09-2015 US 2014275173 A1 18-09-2014 WO 2014151247 A1 25-09-2014
WO 2012078805	A1	14-06-2012	AU 2011338417 A1 25-07-2013 AU 2016238848 A1 27-10-2016 BR 112013013950 A2 27-09-2016 CA 2820884 A1 14-06-2012 CN 103596566 A 19-02-2014 CN 107721940 A 23-02-2018 CY 1120342 T1 10-07-2019 DK 2648726 T3 16-07-2018 EA 201390840 A1 30-10-2013 EP 2648726 A1 16-10-2013 EP 3360552 A1 15-08-2018 ES 2674174 T3 27-06-2018 HR P20180970 T1 10-08-2018 HU E040397 T2 28-03-2019 IL 226698 A 31-05-2018 JP 6030567 B2 24-11-2016 JP 2013544890 A 19-12-2013 KR 20130124524 A 14-11-2013 LT 2648726 T 25-06-2018 MX 347544 B 02-05-2017 NO 2648726 T3 01-09-2018 PL 2648726 T3 31-10-2018 PT 2648726 T 25-06-2018 SG 191041 A1 30-08-2013 SI 2648726 T1 29-06-2018 TR 201809293 T4 23-07-2018 US 2013253023 A1 26-09-2013 US 2017121295 A1 04-05-2017 WO 2012078805 A1 14-06-2012
WO 2017223016	A1	28-12-2017	AR 108838 A1 03-10-2018 AU 2017281439 A1 07-02-2019 BR 112018076558 A2 02-04-2019 CA 3029202 A1 28-12-2017 CL 2018003708 A1 08-02-2019 CN 109963843 A 02-07-2019 CO 2019000471 A2 08-02-2019 EA 201892710 A1 31-05-2019 EP 3472148 A1 24-04-2019 JP 2019518766 A 04-07-2019 KR 20190020049 A 27-02-2019 SG 11201811321T A 30-01-2019

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/051272

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		TW 201808919 A	16-03-2018
		US 2017360759 A1	21-12-2017
		US 2018333395 A1	22-11-2018
		UY 37302 A	02-01-2018
		WO 2017223016 A1	28-12-2017

WO 2013160873 A1	31-10-2013	AP 3592 A	15-02-2016
		AR 090859 A1	10-12-2014
		AU 2013254307 A1	30-10-2014
		BR 112014026760 A2	27-06-2017
		CA 2870336 A1	31-10-2013
		CL 2014002822 A1	24-04-2015
		CN 104395309 A	04-03-2015
		CO 7111275 A2	10-11-2014
		CR 20140494 A	13-03-2015
		EA 201491970 A1	31-03-2015
		EP 2852590 A1	01-04-2015
		ES 2624291 T3	13-07-2017
		JP 6042529 B2	14-12-2016
		JP 2015514798 A	21-05-2015
		KR 20150013194 A	04-02-2015
		MA 37439 A1	29-07-2016
		MX 357768 B	24-07-2018
		PE 07242015 A1	17-05-2015
		PE 08022016 A1	03-09-2016
		PH 12014502413 A1	12-01-2015
		SG 11201406526W A	27-11-2014
		TN 2014000425 A1	30-03-2016
		TW 201348239 A	01-12-2013
		US 2013289058 A1	31-10-2013
		US 2015166563 A1	18-06-2015
		UY 34767 A	29-11-2013
		WO 2013160873 A1	31-10-2013
