

CARBAMOYLOXYMETHYL TRIAZOLE CYCLOHEXYL ACIDS AS
LPA ANTAGONISTS

5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial No. 62/352,792, filed June 21, 2016, the entire content of which is incorporated herein by reference.

10 FIELD OF THE INVENTION

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

15

BACKGROUND OF THE INVENTION

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

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

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

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).

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 substituted triazole compounds including stereoisomers, tautomers, pharmaceutically acceptable salts, solvates or prodrugs thereof,
10 which are 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, solvates or prodrugs thereof.

The compounds of the invention may be used in the treatment and/or prophylaxis 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 and/or prophylaxis 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
25 associated with at 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).

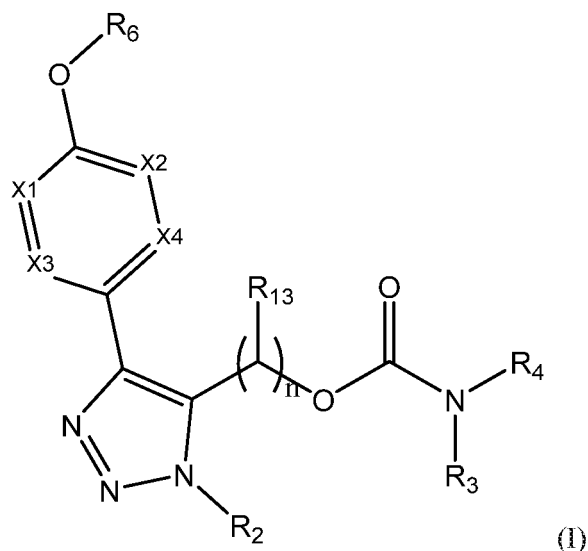
These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

In one aspect, the present invention provides, *inter alia*, compounds of Formula

5 (I):



or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein

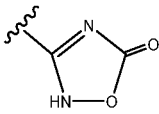
- 10 R_2 is independently selected from H and C_{1-4} alkyl substituted with 1-5 R_9 ;
 R_{13} is independently selected from H, D, and C_{1-4} alkyl substituted with 1-3 R_9 ;
 R_3 and R_4 are independently selected from H, C_{1-7} alkyl substituted with 1-3 R_9 , -
 $(CR_7R_7)_r$ - C_{3-8} cycloalkyl substituted with 1-3 R_8 , $-(CR_7R_7)_r$ -aryl substituted with 1-3 R_8 ,
 C_{2-7} alkenyl substituted with 1-3 R_9 , $-(CR_7R_7)_r$ -5-6 membered heterocyclic ring substituted
15 with 1-3 R_8 , $-(CR_7R_7)_r$ -5-6 membered heteroaryl ring substituted with 1-3 R_8 , or R_3 and
 R_4 combine with the N to which they are attached to form a 4-9 membered heterocyclic
ring substituted with 1-3 R_8 ;
 X^1 , X^2 , X^3 , and X^4 are independently selected from CR_5 and N; provided no more than
two of X^1 , X^2 , X^3 , or X^4 are N;
20 R_5 is independently selected from H, F, Cl, OR_7 , CN, $N(R_7)_2$, C_{1-4} alkyl substituted with
1-5 R_9 , C_{1-4} alkoxy substituted with 1-5 R_9 , and C_{1-4} heteroalkyl substituted with 1-5 R_9 ;
 R_6 is C_{3-8} cycloalkyl which is substituted with R_{10} and $(-CH_2)_{0-1}R_{11}$;

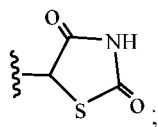
R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

R₈ is independently selected from H, D, C₁₋₆ alkyl substituted with 1-5 R₉, C₂₋₆ alkenyl, C₂₋₆ alkynyl, phenyl, -(CH₂)_r-C₃₋₆ cycloalkyl, F, Cl, Br, CN, COOH, and C₁₋₄ alkoxy;

- 5 R₉ is independently selected from H, D, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₁₋₅ heteroalkyl C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H, D, C₁₋₄ alkyl, F, Cl, Br, OR₇, NHC(=O)OR₇, and NHC(=O)OR₇;

- 10 R₁₁ is independently selected from H, CN, -C(=O)R₁₂, tetrazolyl, , and



R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, NHCH₂CH₂SO₃H, and NHSO₂C₁₋₄alkyl;

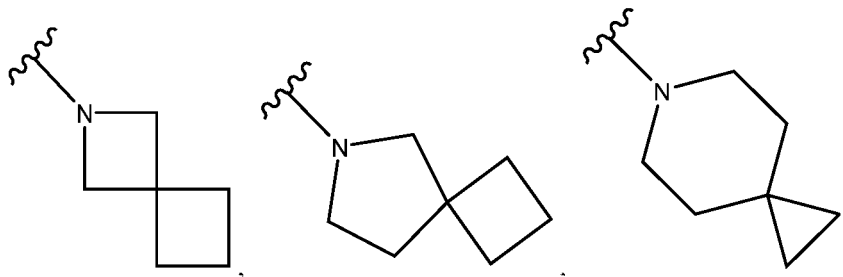
r is independently selected from zero, 1, 2, 3, and 4,

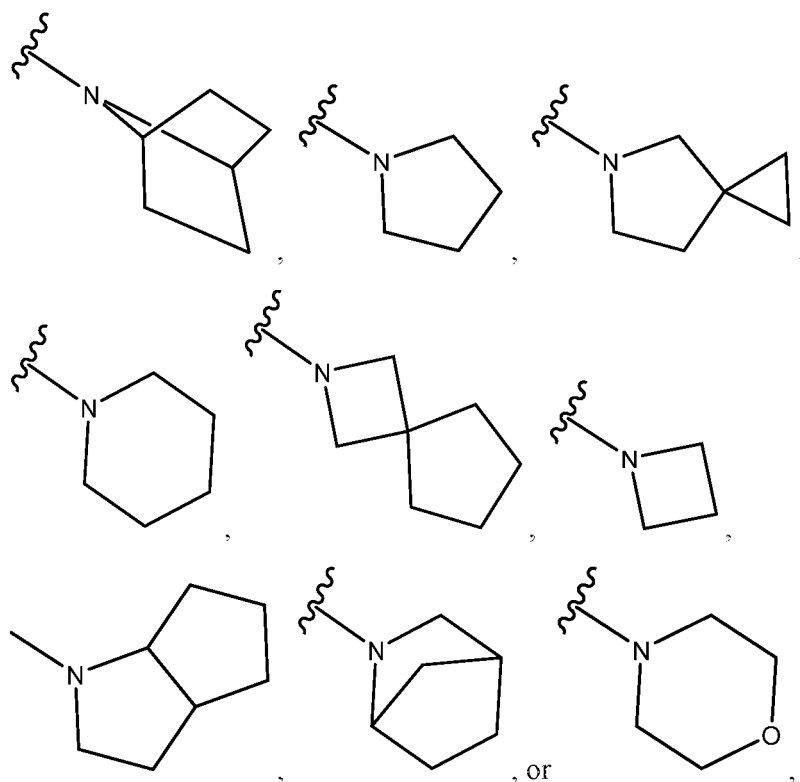
- 15 and n is selected from 1, 2, 3, or 4.

In another embodiment, the present invention includes compounds of Formula (I), wherein

R₃ and R₄ are independently selected from H, C₁₋₇ alkyl substituted with 1-3 R₉, - (CR₇R₇)_r-C₃₋₈ cycloalkyl substituted with 1-3 R₈, -(CR₇R₇)_r-aryl substituted with 1-3 R₈,

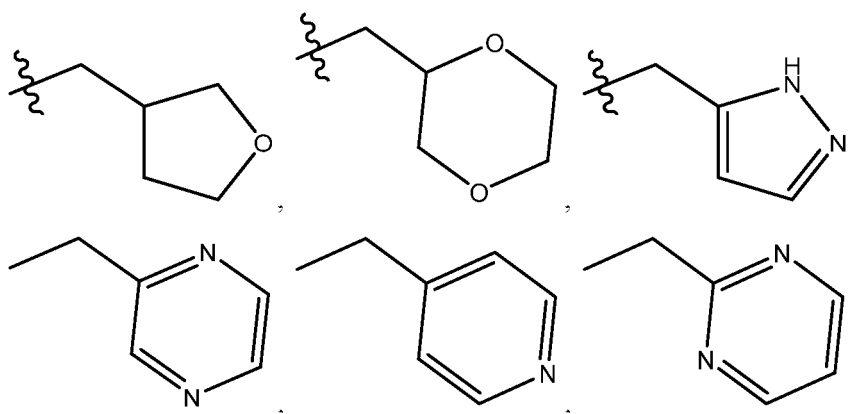
- 20 C₂₋₇alkenyl substituted with 1-3 R₉, -(CR₇R₇)_r-5-6 membered heterocyclic ring substituted with 1-3 R₈, -(CR₇R₇)_r-5-6 membered heteroaryl ring substituted with 1-3 R₈, and R₃ and R₄ combine with the N to which they are attached to form the following:

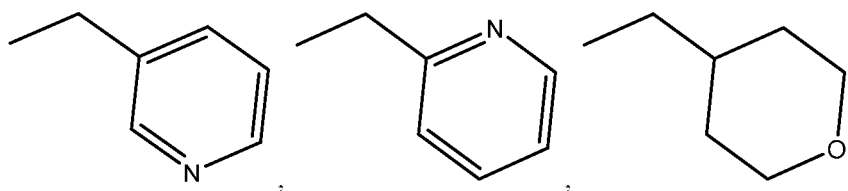




5 may be substituted with 1-3 R_8 , and
 n equals 1 or 2.

In another embodiment, the present invention includes compounds of Formula (I)
 wherein, R_3 and R_4 are independently selected from H, C_{1-7} alkyl substituted with 1-3 R_9 ,
 $-(CR_7R_7)_i-C_{3-8}$ cycloalkyl substituted with 1-3 R_8 , $-(CR_7R_7)_i$ -aryl substituted with 1-3 R_8 ,
 10 C_{2-7} alkenyl substituted with 1-3 R_9 ,

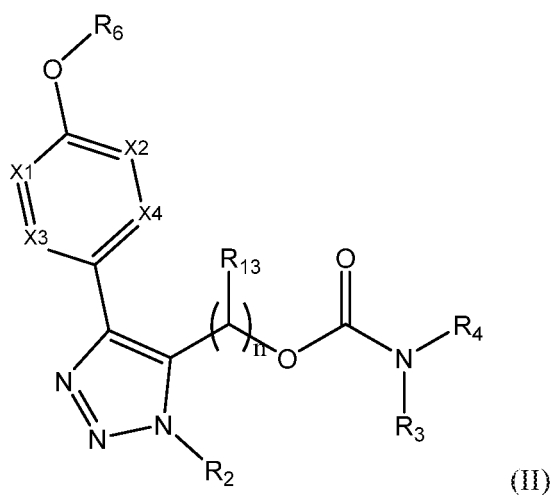




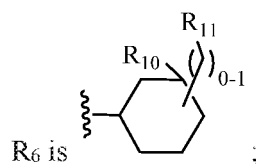
each of which can be substituted with 1-3 R_8 , and R_3 and R_4 combine with the N to which they are attached to form a 4-9 membered heterocyclic ring substituted with 1-3 R_8 ; and

5 n equals 1 or 2.

In another embodiment, the present invention includes compounds of Formula (II):



- 10 or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein
- R_2 is independently selected from H and C_{1-4} alkyl substituted with 1-5 R_9 ;
- R_{13} is independently selected from H, D, and C_{1-4} alkyl substituted with 1-3 R_9 ;
- R_3 and R_4 are independently selected from H, C_{1-7} alkyl substituted with 1-3 R_9 ,
- 15 $-(CR_7R_7)_1-C_{3-6}$ cycloalkyl substituted with 1-3 R_8 , and $-(CR_7R_7)_1$ -aryl substituted with 1-3 R_8 ;
- X^1 , X^2 , X^3 , and X^4 are independently selected from CR_5 and N; provided no more than two of X^1 , X^2 , X^3 , or X^4 are N;
- R_5 is independently selected from H, F, Cl, OR_7 , CN, $N(R_7)_2$, C_{1-4} alkyl substituted with
- 20 1-5 R_9 , C_{1-4} alkoxy substituted with 1-5 R_9 , and C_{1-4} heteroalkyl substituted with 1-5 R_9 ;

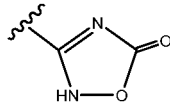


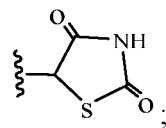
R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_r-C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and CO₂H;

R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅ heteroalkyl C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H, D, C₁₋₄ alkyl, F, Cl, Br, OR₇, NHC(=O)OR₇, and NHC(=O)R₇;

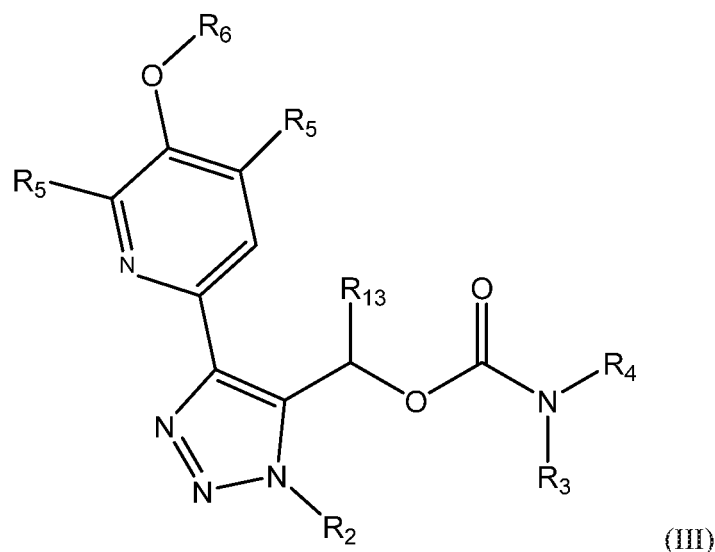
R₁₁ is independently selected from CN, -C(=O)R₁₂, tetrazolyl, , and



R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, NHCH₂CH₂SO₃H, and NHSO₂C₁₋₄alkyl; and

r is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides compounds of Formula (III):



or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

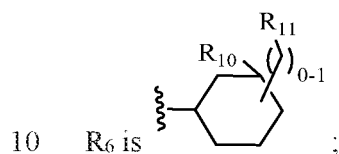
5 R₁₃ is independently selected from H and C₁₋₄ alkyl;

R₃ is independently selected from H and C₁₋₄ alkyl;

R₄ is independently selected from C₁₋₆ alkyl substituted with 1-3 R₉, -(CR₇R₇)_r-C₃₋₆

cycloalkyl substituted with 1-3 R₈, and -(CR₇R₇)_r-aryl substituted with 1-3 R₈;

R₅ is independently selected from H, F, Cl, CN and C₁₋₄ alkyl; provided one of R₅ is H;



R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and COOH;

15 R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

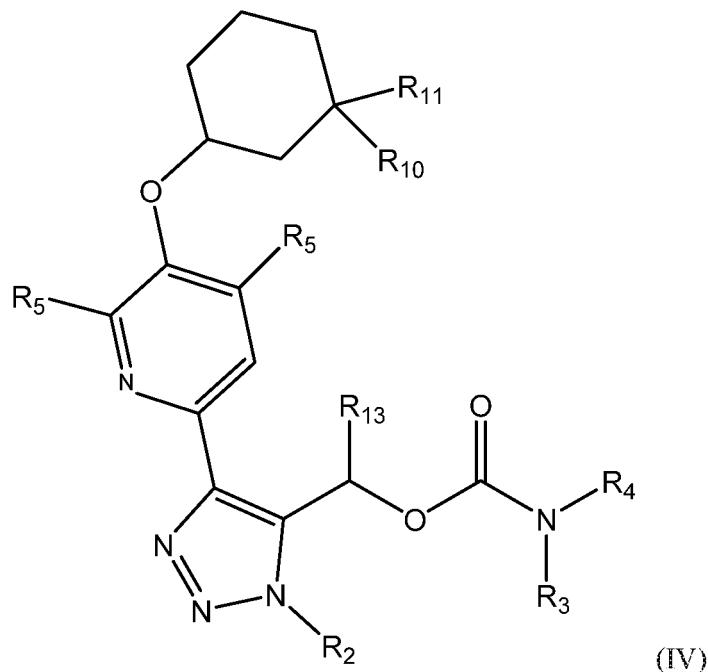
R₁₀ is independently selected from H, D, C₁₋₄ alkyl, and F;

R₁₁ is independently selected from CN, -C(=O)R₁₂, and tetrazolyl;

20 R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, and NHSO₂C₁₋₄alkyl; and

r is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides compounds of Formula (IV):



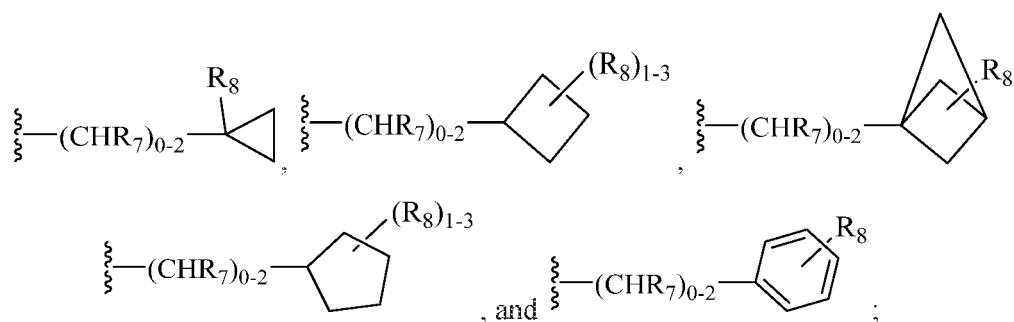
5 or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

R₁₃ is independently selected from H and C₁₋₄ alkyl;

R₃ is independently selected from H and C₁₋₄ alkyl;

10 R₄ is independently selected from C₁₋₆ alkyl,



R₅ is independently selected from H, F, Cl, and C₁₋₄ alkyl; provided one of R₅ is H;

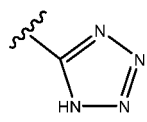
R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl;

15 R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and COOH;

R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H, D, C₁₋₄ alkyl, and F;

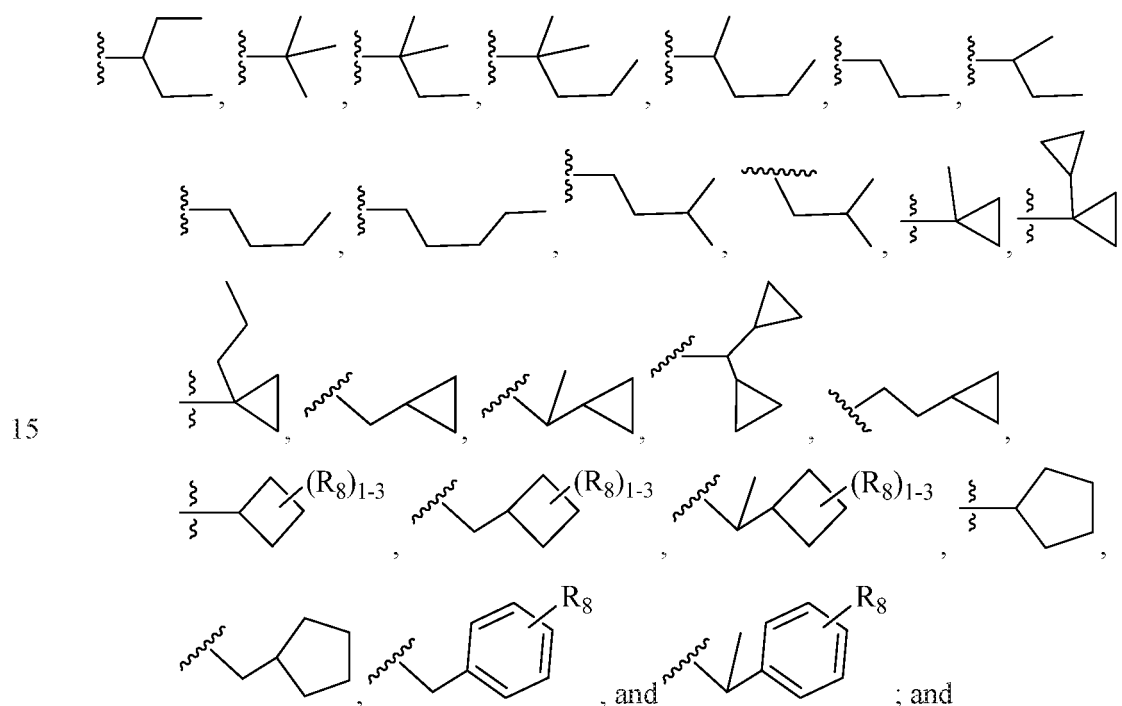
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R₁₁ is independently selected from CN, -C(=O)R₁₂, and ; and

R₁₂ is independently selected from OH, NH₂ and NHSO₂C₁₋₄alkyl.

In another aspect, the present invention provides compounds of Formula (III) or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

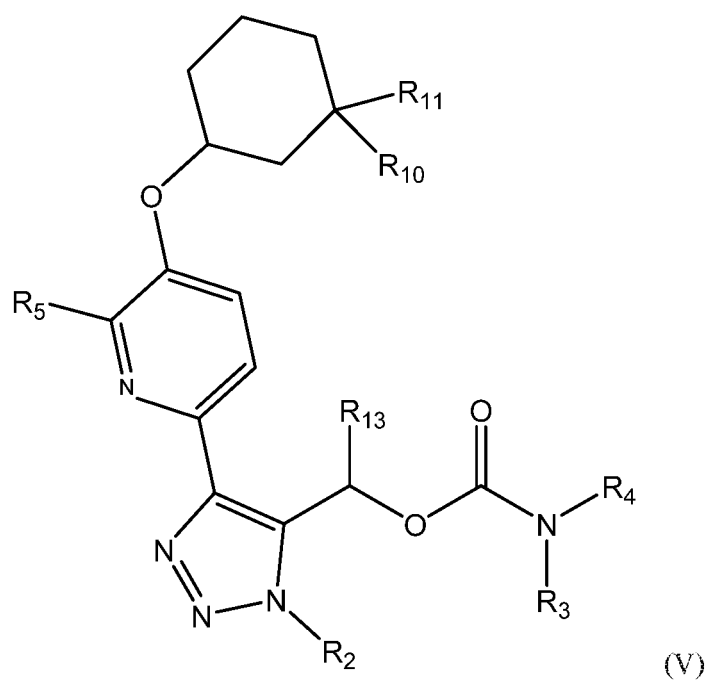
10 R₄ is independently selected from



R₈ is independently selected from H, F, Cl, Br, CN, and C₁₋₄ alkyl; and other variables are as defined in Formula (IV).

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In another aspect, the present invention provides compounds of Formula (V):



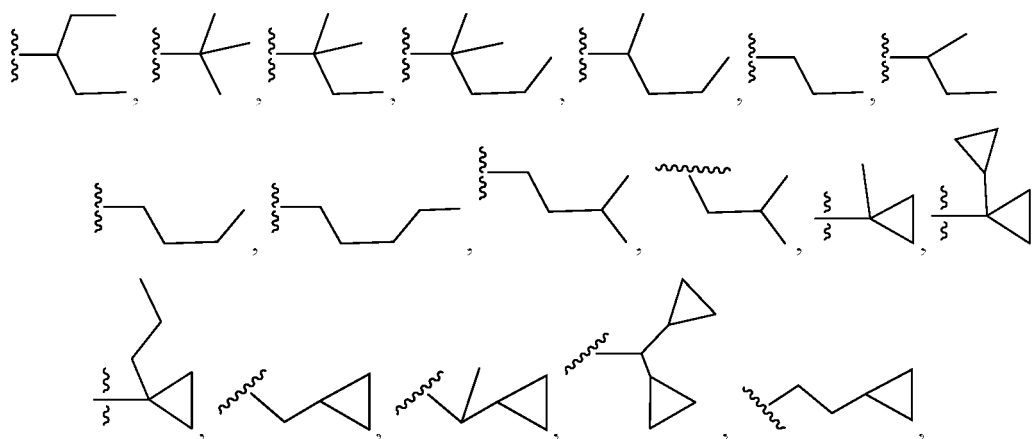
or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

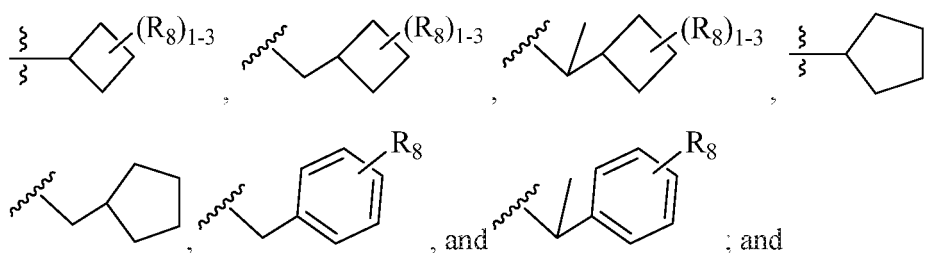
5 R₂ is independently selected from CH₃ and CD₃;

R₁₃ is independently selected from H and CH₃;

R₃ is independently selected from H and CH₃;

R_4 is independently selected from





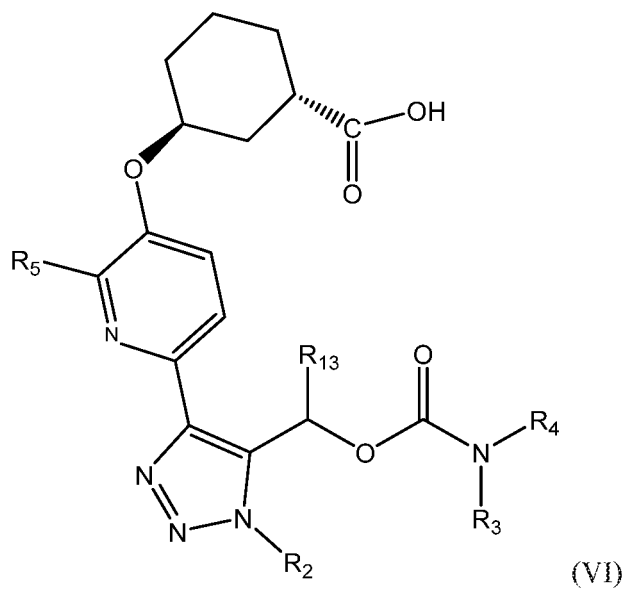
R₅ is independently selected from H, F, and C₁₋₄ alkyl;

R₈ is independently selected from H, F, Cl, Br, CN, and C₁₋₄ alkyl;

5 R₁₀ is independently selected from H, D, and F; and

R₁₁ is independently selected from -C(=O)OH, and -C(=O)NHSO₂Me.

In another aspect, the present invention provides compounds of Formula (VI):



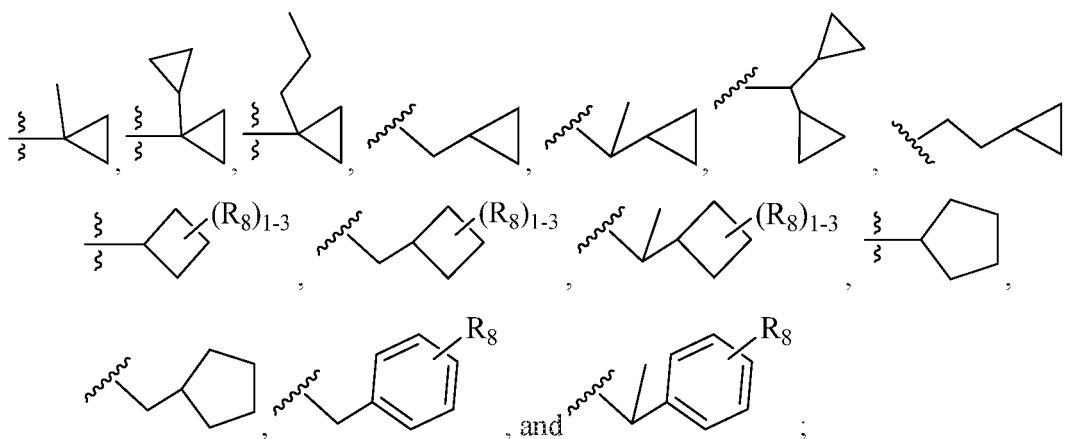
10 or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

R₁₃ is independently selected from H and CH₃;

R₃ is independently selected from H and CH₃;

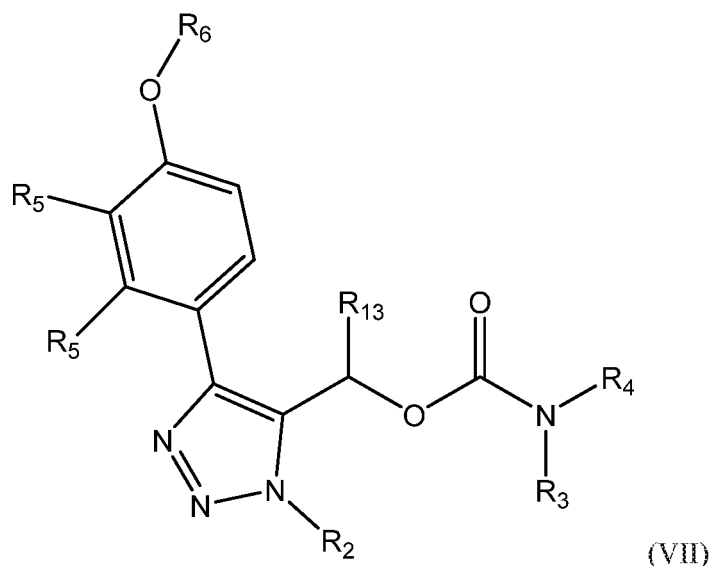
15 R₄ is independently selected from



R_5 is independently selected from H and CH_3 ; and

- 5 R_8 is independently selected from H, F, Cl, Br, CN, and C_{1-4} alkyl.

In another aspect, the present invention provides compounds of Formula (VII):



or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs

- 10 thereof, wherein

R_2 is independently selected from CH_3 and CD_3 ;

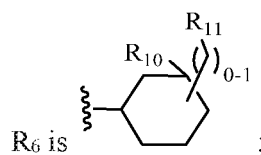
R_{13} is independently selected from H and C_{1-4} alkyl;

R_3 is independently selected from H and C_{1-4} alkyl;

R_4 is independently selected from C_{1-6} alkyl substituted with 1-3 R_9 , $(CR_7R_7)_r-C_{3-6}$

- 15 cycloalkyl substituted with 1-3 R_8 , and $-(CR_7R_7)_r$ -aryl substituted with 1-3 R_8 ;

R_5 is independently selected from H, F, Cl, CN, and C_{1-4} alkyl;

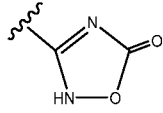


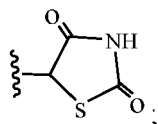
R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

5 R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and COOH;

R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H, C₁₋₄ alkyl, and F;

10 R₁₁ is independently selected from CN, -C(=O)R₁₂, tetrazolyl, , and



R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, NHCH₂CH₂SO₃H, and NHSO₂C₁₋₄alkyl; and

r is independently selected from zero, 1, 2, 3, and 4.

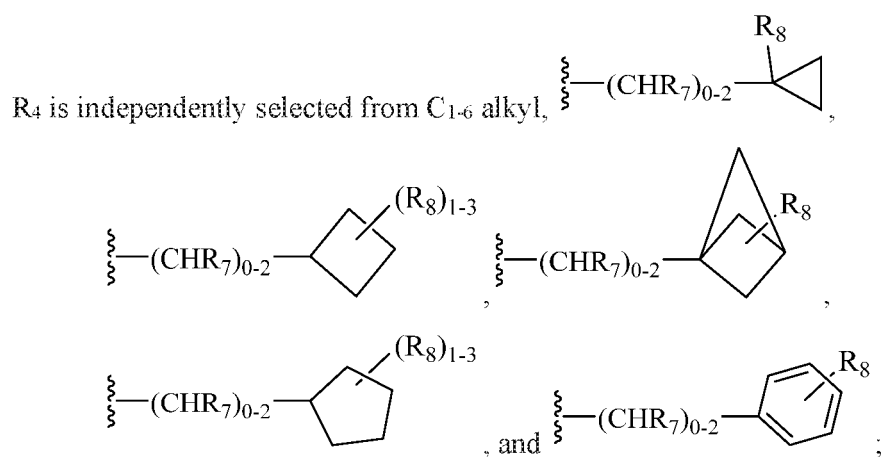
15

In another aspect, the present invention provides compounds of Formula (VI) or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R₁ is independently selected from CH₃ and CD₃;

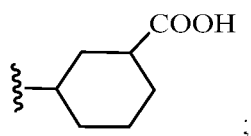
20 R₂ is independently selected from H and CH₃;

R₃ is independently selected from H and CH₃;



R₅ is independently selected from H, F, Cl, and C₁₋₄ alkyl;

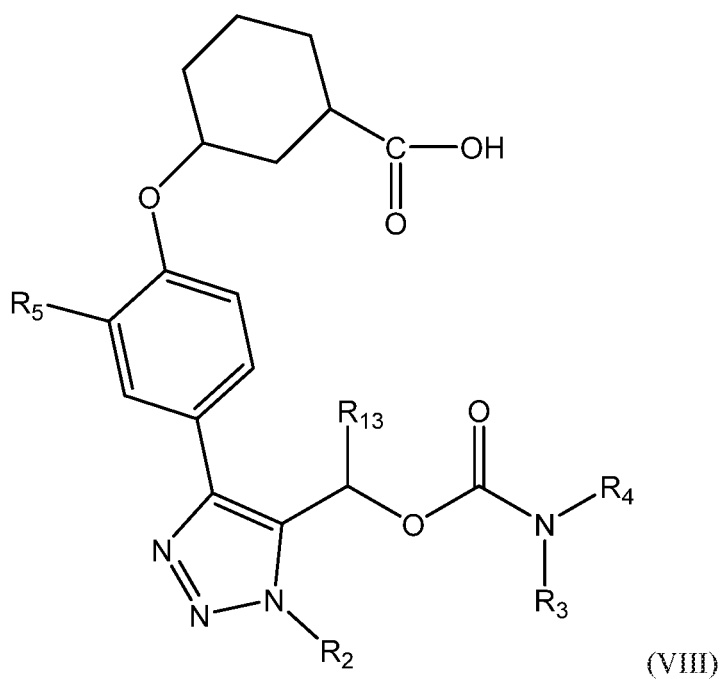
5 R₆ is



R₇ is independently selected from H, C₁₋₄ alkyl, and C₁₋₆ cycloalkyl; and

R₈ is independently selected from H, F, Cl, Br, CN, and C₁₋₄ alkyl.

10 In another aspect, the present invention provides compounds of Formula (VIII):



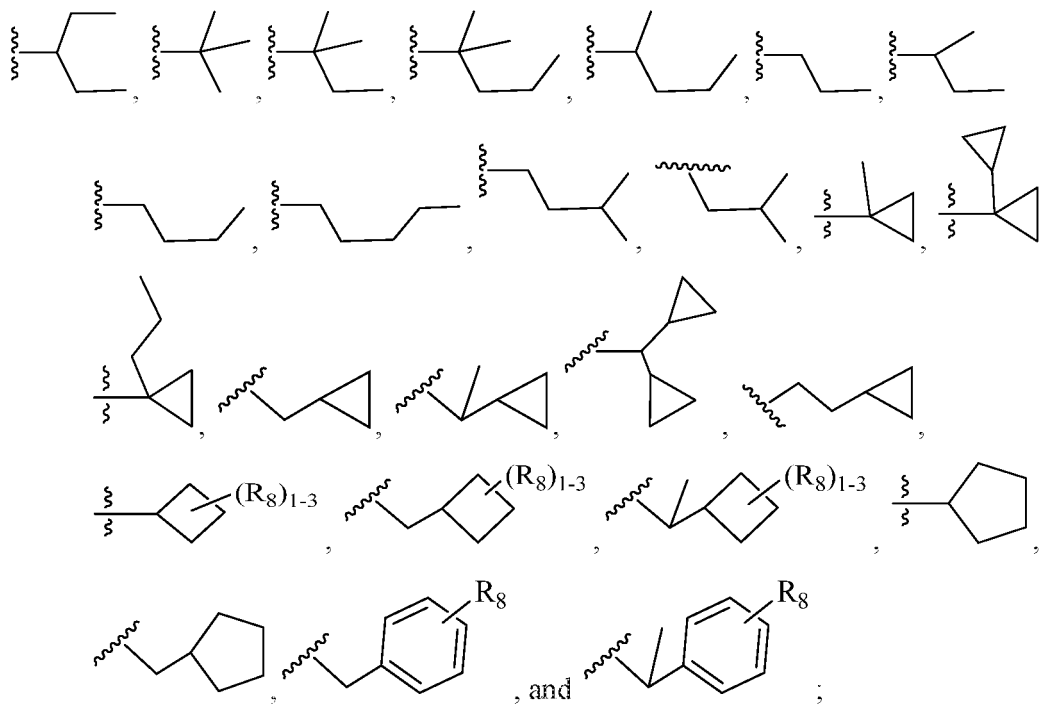
or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

R₁₃ is independently selected from H and CH₃;

5 R₃ is independently selected from H and CH₃;

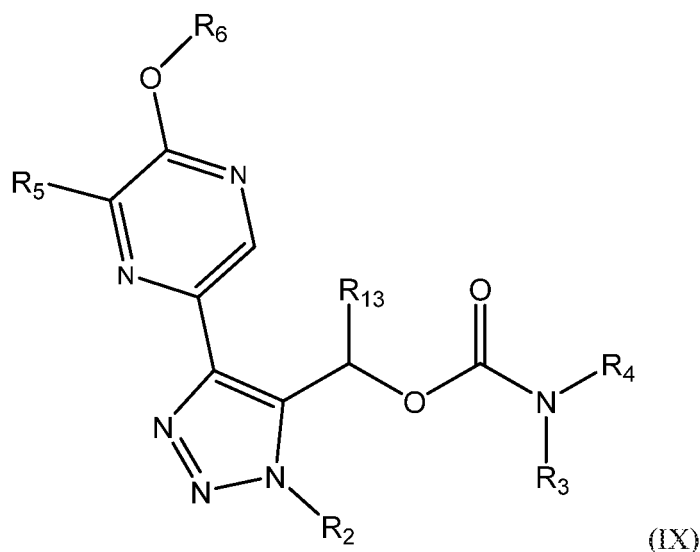
R_4 is independently selected from



R₅ is independently selected from H, F, and CH₃; and

R₈ is independently selected from H, F, Cl, Br, CN, and C₁₋₄ alkyl.

15 In another aspect, the present invention provides compounds of Formula (IX):



or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

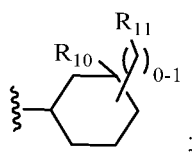
5 R₁₃ is independently selected from H and C₁₋₄ alkyl;

R₃ is independently selected from H and C₁₋₄ alkyl;

R₄ is independently selected from C₁₋₆ alkyl substituted with 1-3 R₉, (CR₇R₇)_r-C₃₋₆ cycloalkyl substituted with 1-3 R₈, and -(CR₇R₇)_r-aryl substituted with 1-3 R₈;

R₅ is independently selected from H, F, Cl, CN, and C₁₋₄ alkyl;

10 R₆ is independently selected from



R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

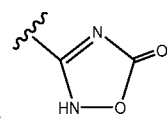
R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and COOH;

15

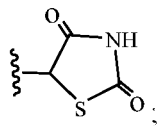
R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H, and F,

R₁₁ is independently selected from CN, -C(=O)R₁₂, tetrazolyl,



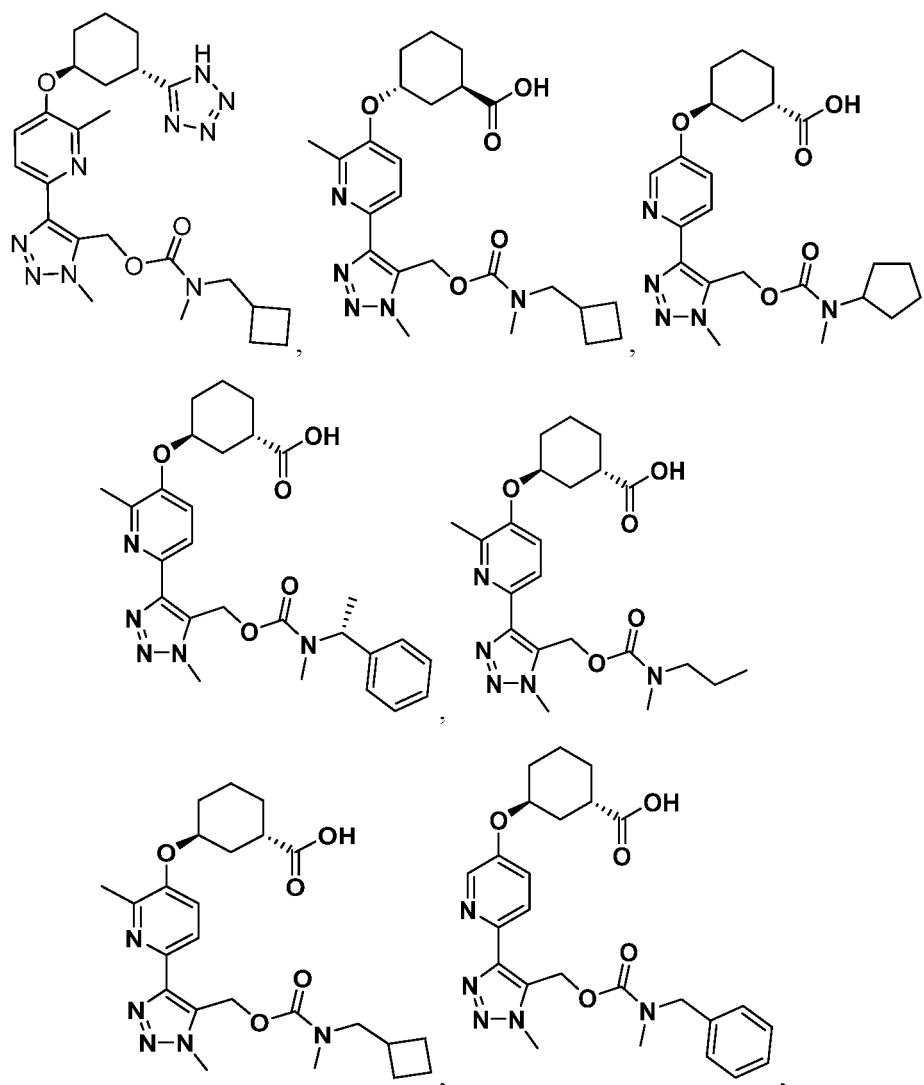
, and



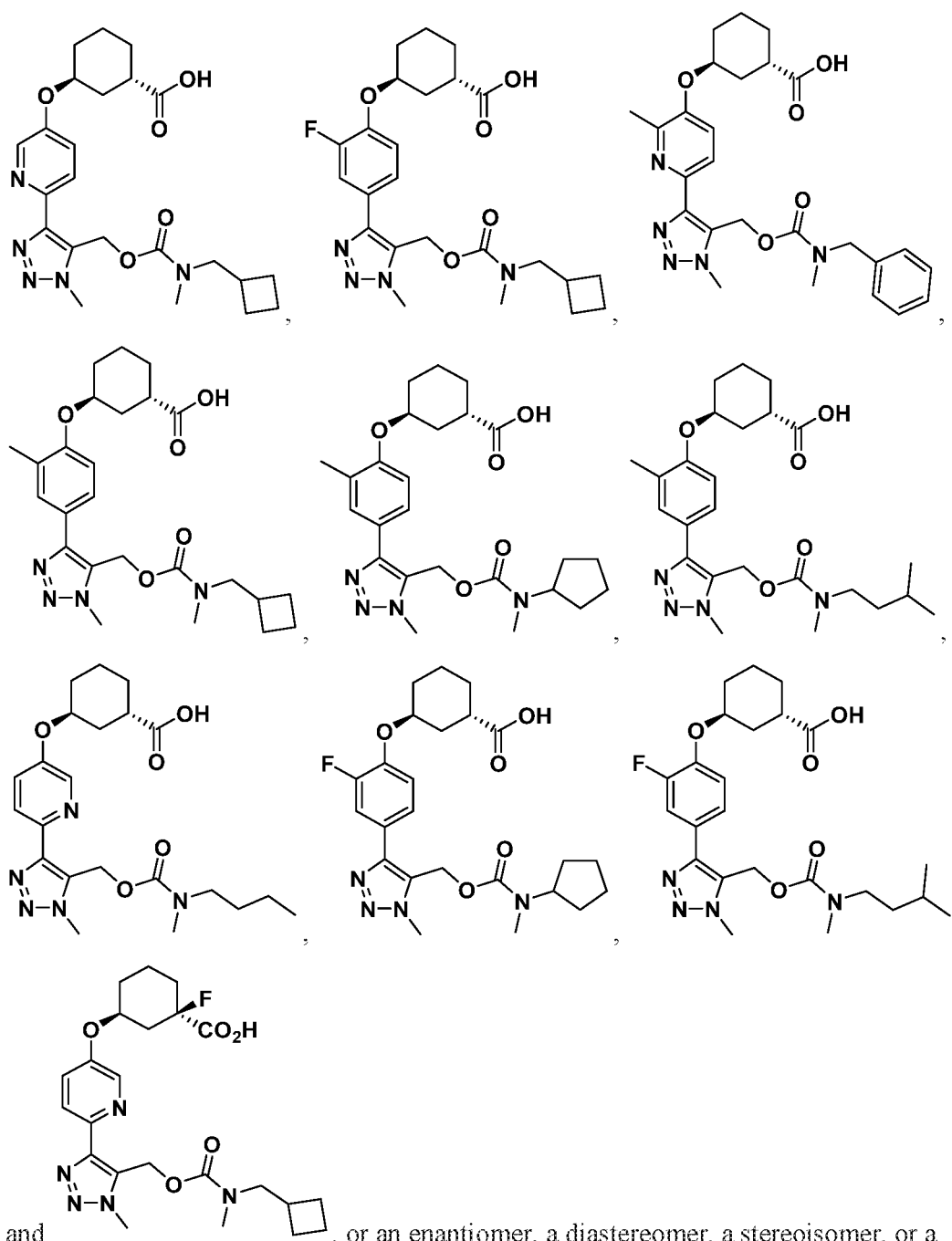
R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, NHCH₂CH₂SO₃H, and
NHSO₂C₁₋₄alkyl; and

5 r is independently selected from zero, 1, 2, 3, and 4.

In yet another embodiment, the present invention includes a compound of
Formula (I) or (II) selected from the group of:



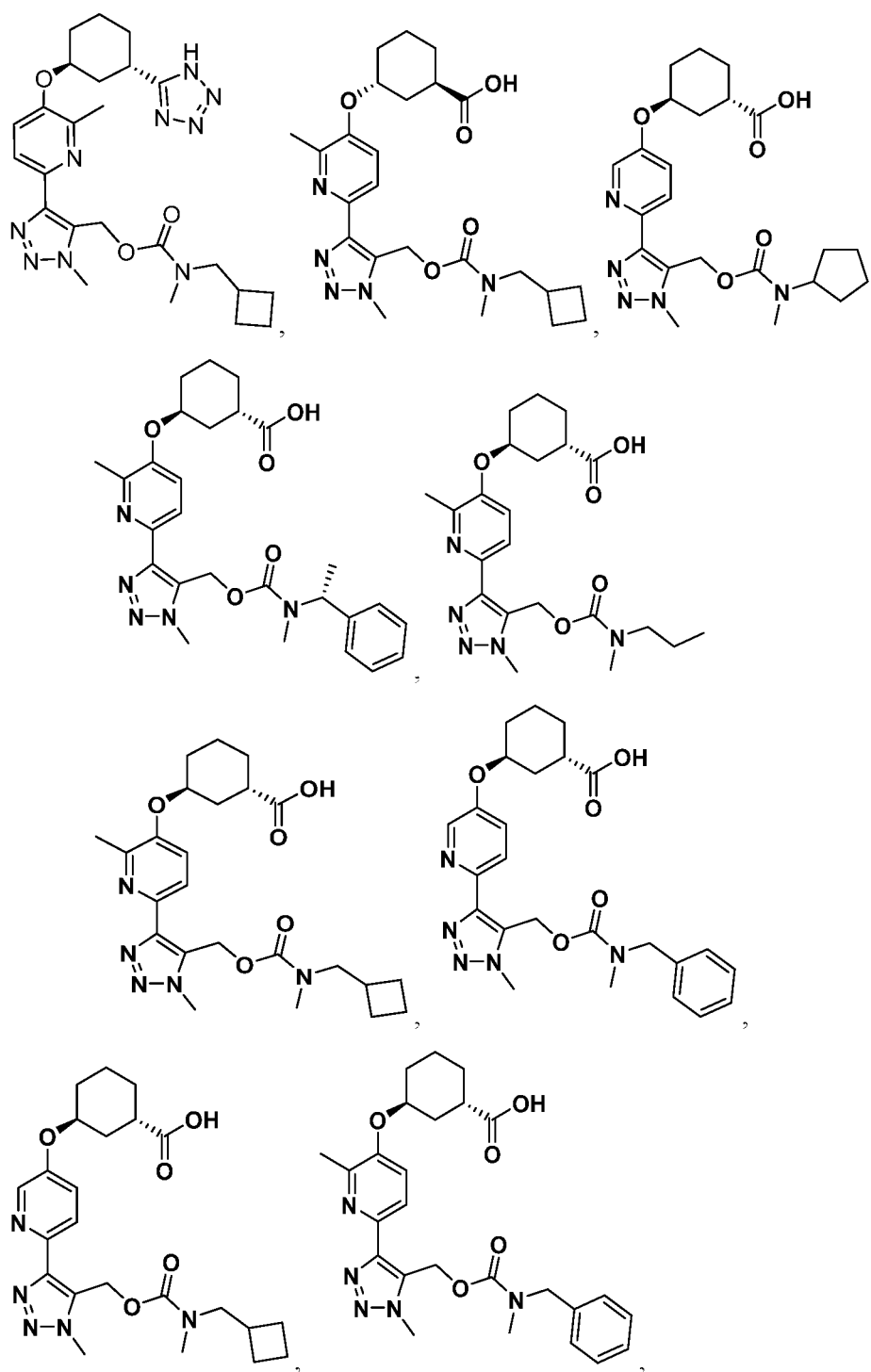
10

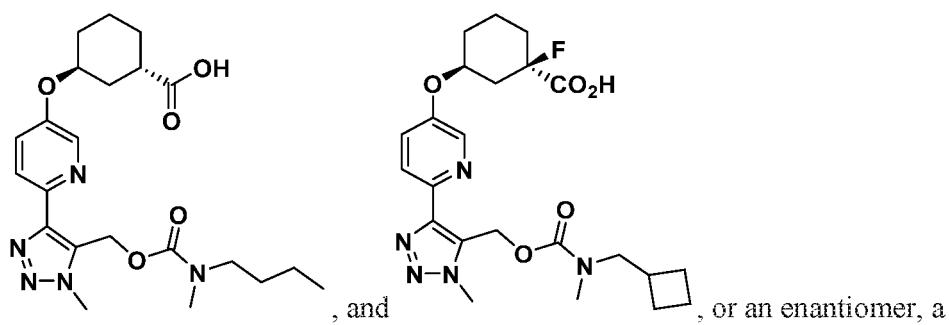


5

pharmaceutically acceptable salt thereof.

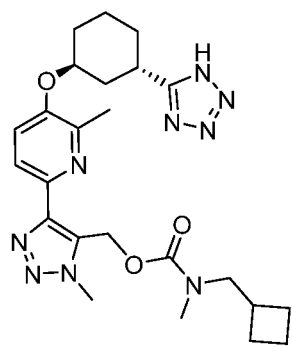
In yet another embodiment, the present invention includes a compound of Formula (I) or (II) selected from the group of:





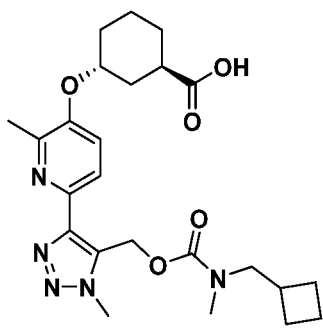
diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



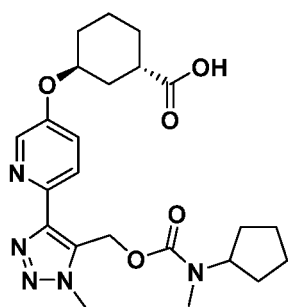
5 , an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



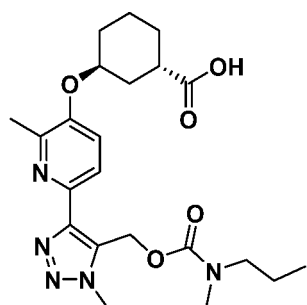
10 or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



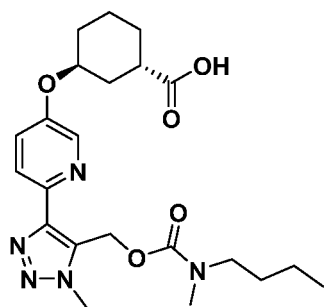
, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



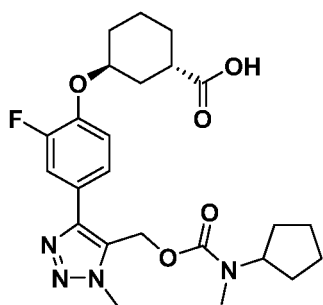
5 , an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



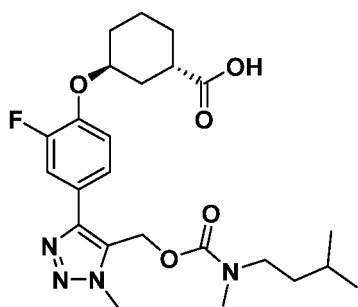
10 , an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



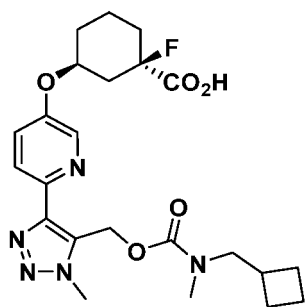
, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



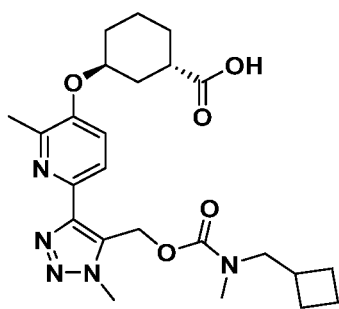
5 , an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



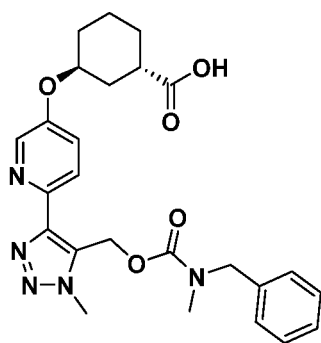
10 , or an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

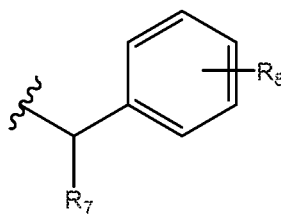
In yet another embodiment, the present invention includes compound of Formula (I) or (II) wherein said compound has the formula:



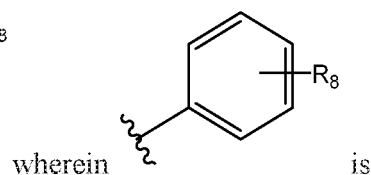
5 , an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments, R_{12} is -OH, -OC₁₋₄ alkyl, or -NHSO₂C₁₋₄ alkyl. In some embodiments, R_{12} is -OH or -OC₁₋₄ alkyl. In some
10 embodiments, R_{12} is -OH. In some embodiments, R_{12} is -OC₁₋₄ alkyl. In some embodiments, R_{12} is -OCH₃ or -OCH₂CH₃. In some embodiments, R_{12} is -NHSO₂C₁₋₄ alkyl.

In some embodiments, R_3 is C₁₋₄ alkyl; R_5 is H or C₁₋₄ alkyl. In some
embodiments, R_{12} is -OH, -OCH₃, -OCH₂CH₃, -NHSO₂CH₃ or -NHSO₂CH₂CH₃; R_3 is -
15 CH₃, CD₃ or -CH₂CH₃. In some embodiments, R_{12} is -OH, -OCH₃, -OCH₂CH₃, -NHSO₂CH₃ or -NHSO₂CH₂CH₃; R_3 is -CH₃, CD₃, or -CH₂CH₃; R_5 is H or C₁₋₄ alkyl.



In some embodiments, R_4 is



wherein

is

2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-

ethylphenyl, 2-deuteromethylphenyl, 3-deuteromethylphenyl, 4-deuteromethylphenyl, 2-monofluoromethylphenyl, 3-monofluoromethylphenyl, 4-monofluoromethylphenyl, 2-difluoromethylphenyl, 3-difluoromethylphenyl, 4-difluoromethylphenyl, 2-cyclopropylphenyl, 3-cyclopropylphenyl, 4-cyclopropylphenyl, 2-cyclobutylphenyl, 3-cyclobutylphenyl, 4-cyclobutylphenyl, 2-cyclopentylphenyl, 3-cyclopentylphenyl, 4-cyclopentylphenyl, 2-cyclohexylphenyl, 3-cyclohexylphenyl or 4-cyclohexylphenyl.

In some embodiments, R_4 is $-(CHR_7)_r-C_{3-6}$ cycloalkyl and r is 0, 1, or 2, and R_7 is H or methyl. In some embodiments, r is 0, R_4 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl and R_7 is H or methyl. In some embodiments, r is 1, R_4 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, R_7 is H or methyl.

In some embodiments, R_3 is C_{1-4} alkyl, R_4 is $-(CHR_7)_r-C_{3-6}$ cycloalkyl, and r is 0, 1, or 2, and R_7 is H or methyl. In some embodiments, R_3 is $-CH_3$, CD_3 , or $-CH_2CH_3$, R_4 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, r is 0 or 1, and R_7 is H or methyl. In some embodiments, R_3 is $-CH_3$, R_4 is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, r is 1, R_7 is H or methyl.

In some embodiments, R_3 is C_{1-4} alkyl, R_4 is C_{1-4} alkyl, and R_7 is H or methyl. In some embodiments, R_3 is $-CH_3$, CD_3 , or $-CH_2CH_3$, R_4 is $-CH_3$, CD_3 , $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-CH(CH_3)_3$, and R_7 is H or methyl. In some embodiments, R_3 is $-CH_3$, R_4 is $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-CH(CH_3)_3$, R_7 is H or methyl.

In some embodiments, R_1 is H or C_{1-2} alkyl, R_2 is H or C_{1-2} alkyl, R_3 is C_{1-2} alkyl, R_4 is $-(CHR_7)_r-C_{3-6}$ cycloalkyl and r is 1, R_5 is H or C_{1-2} alkyl, R_6 is cyclopentyl or cyclohexyl, R_7 is H or C_{1-2} alkyl, R_8 is H, R_9 is H, R_{10} is H, and R_{11} is $-C(=O)OH$.

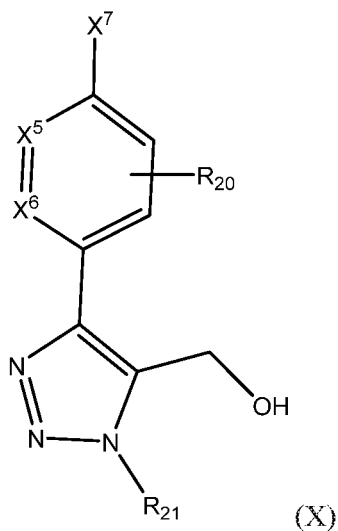
In some embodiments, R_1 is H or methyl, R_2 is H or methyl, R_3 is methyl, R_4 is $-CHR_7$ -cyclopropyl, $-CHR_7$ -cyclobutyl, $-CHR_7$ -cyclopentyl, or $-CHR_7$ -cyclohexyl, R_5 is H or methyl, R_6 is cyclohexyl, R_7 is H or methyl, R_8 is H, R_9 is H, R_{10} is H, and R_{11} is $-C(=O)OH$.

In some embodiments, the pharmaceutically acceptable salt of the compound of Formulas (I) - (IX) is a sodium salt.

Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

In another aspect, the present invention provides a compound selected from any subset list of compounds exemplified in the present application.

In another embodiment, the present invention includes compounds of Formula (X):



5

or an enantiomer, a diastereomer, or a stereoisomer thereof, wherein

R₂₀ is independently selected from C₁₋₆ alkyl or H;

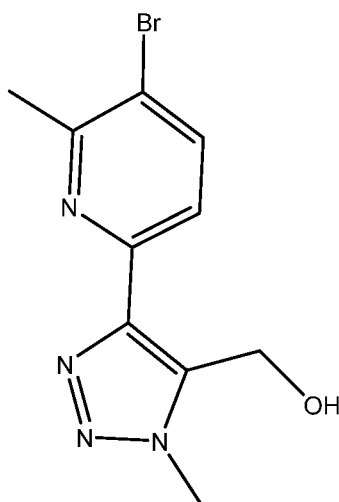
R₂₁ is independently selected from C₁₋₆ alkyl or H;

X⁵ and X⁶ are independently selected from CH or N; and

10

X⁷ is selected from Cl, Br, or F.

In another embodiment, the present invention includes compounds of Formula (XI):



(XI), or an enantiomer,

a diastereomer, or a stereoisomer thereof.

In another aspect, the present invention provides a compound selected from the list below:

- 5 (1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (1)
- (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (2)
- (1S,3S)-3-((6-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (3)
- 10 *trans*-3-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (4)
- (1S,3S)-3-(4-(5-(((Cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylic acid (5)
- 15 (1R,3R)-3-(4-(5-(((Cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylic acid (6)
- (1-Methyl-4-(4-(((1S,3S)-3-((methylsulfonyl)carbamoyl)cyclohexyl)oxy)phenyl)-1H-1,2,3-triazol-5-yl)methyl cyclopentyl(methyl)carbamate (7)
- No names for (8) and (9)
- 20 (1S,3S)-3-(4-(1-Methyl-5-(((methyl(2-methylpentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylic acid (10)
- 3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid (11)

- (1S,3S)-3-(4-(5-(1-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (12)
- 3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid (13)
- 5 (4-(5-(((1S,3S)-3-carbamoylcyclohexyl)oxy)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate (14)
- (4-(5-(((1S,3S)-3-cyanocyclohexyl)oxy)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate (15)
- (4-(5-(((1S,3S)-3-(1H-tetrazol-5-yl)cyclohexyl)oxy)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate (16)
- 10 (1-methyl-4-(6-methyl-5-(((1S,3S)-3-((methylsulfonyl)carbamoyl)cyclohexyl)oxy)pyridin-2-yl)-1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate (17)
- 3-((6-(5-(((cyclopentyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (18),
- 15 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((R)-1-phenylethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (19),
- (1S,3S)-3-((6-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (20),
- 20 (1S,3S)-3-((6-(1-methyl-5-(((methyl((R)-1-phenylethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (21),
- (1S,3S)-3-((6-(5-(((benzyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (22),
- 25 (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (23),
- (1S,3S)-3-((6-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (24),
- (1S,3S)-3-((6-(5-((((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (25),
- 30 (1S,3S)-3-(4-(5-(((benzyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid (26),

(1S,3S)-3-(4-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid (27),

(1S,3S)-3-(2-fluoro-4-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (28),

5 (1S,3S)-3-((6-(5-(((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (29),

(1S,3S)-3-((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (30),

10 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (31),

(1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (32),

15 (1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (33),

(1S,3S)-3-((6-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (34),

20 (1S,3S)-3-((6-(5-(((4-chlorobenzyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (35),

(1S,3S)-3-(4-(5-(((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid (36),

(1S,3S)-3-(4-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid (37),

25 (1S,3S)-3-(4-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid (38),

(1S,3S)-3-(2-methyl-4-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (39),

30 (1S,3S)-3-(4-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid (40),

- (1S,3S)-3-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid (41),
- (1S,3S)-3-((6-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-4-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (42),
- 5 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (43),
- (1S,3S)-3-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid (44),
- (1S,3S)-3-(4-(5-(((1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid (45),
- 10 (1S,3S)-3-(4-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid (46),
- (1S,3S)-3-(2-fluoro-4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (47),
- 15 (1S,3S)-3-(4-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (isomer 1) (48),
- (1S,3S)-3-(4-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (isomer 2) (49),
- (1S,3S)-3-((6-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (50),
- 20 (1S,3S)-3-(4-(5-((((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (51),
- (1S,3S)-3-(4-(5-((((S)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (52),
- 25 (1S,3S)-3-(4-(5-(((isobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (53),
- (1S,3S)-3-(4-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (54),
- (1S,3S)-3-(4-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (55),
- 30 (1S,3S)-3-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid (56),

(1S,3S)-3-(4-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (57),

(1S,3S)-3-(4-(1-methyl-5-(((methyl(pentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (58),

5 (1S,3S)-3-(4-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (59),

(1S,3S)-3-(4-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (60),

10 (1S,3S)-3-(4-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (61),

(1R,3R)-3-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (62),

(1R,3R)-3-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid (63),

15 (1S,3S)-3-(4-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (64),

(1S,3S)-3-(4-(5-(((1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (65),

20 (1S,3S)-3-(4-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (66),

(1S,3S)-3-(4-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (67),

(1S,3S)-3-(4-(5-(((sec-butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (68),

25 (3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic-1-d acid (69),

(1S,3S)-3-(4-(5-(((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid (70),

30 (1S,3S)-3-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (71),

(1-Methyl-4-(4-(((1R,3R)-3-((methylsulfonyl)carbamoyl)cyclohexyl)oxy)phenyl)-1H-1,2,3-triazol-5-yl)methyl cyclopentyl(methyl)carbamate (72),

(1S,3S)-3-(4-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (73),

(1S,3S)-3-(4-(5-(((Dicyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylic acid (74),

5 (1S,3S)-3-(4-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (75),

(1S,3S)-3-(4-(1-methyl-5-(((methyl(pentan-3-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (76),

10 (1S,3S)-3-((6-(1-methyl-5-(((methyl(pentan-3-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (77),

(1S,3S)-3-((6-(1-methyl-5-(((methyl(2-methylpentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (78),

15 (1S,3S)-3-((6-(1-methyl-5-(((methyl(1-methylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (79),

(1S,3S)-3-((6-(5-(((Dicyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexanecarboxylic acid (80),

20 (1S,3S)-3-((6-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (81, 82),

(1S,3S)-3-((2-Methyl-6-(1-methyl-5-(((methyl(pentan-3-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexanecarboxylic acid (83),

25 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(2-methylpentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexanecarboxylic acid (84),

30 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-methylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (85),

(1S,3S)-3-((6-(5-(((Dicyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylic acid (86),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (87),

(rac)-trans-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid (88),

trans-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid (89),

trans-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid (90),

trans-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (91),

cis-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (92),

cis-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclopentane-1-carboxylic acid (93),

(1S,3S)-3-(4-(5-(1-((cyclopentyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (94),

(Cis)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (Enantiomer A, 95),

(Cis)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (Enantiomer B, 96),

(1R,3R)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (97),

(1S,3S)-3-((6-(5-(((2-fluorobenzyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (98),

(1S,3S)-3-((6-(5-(((1-cyclobutylpropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (99),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-phenylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (100),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(3,3,3-trifluoropropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (101),

(1S,3S)-3-((6-(5-(((bicyclo[1.1.1]pentan-1-yl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (102),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(phenethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (103),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (104),

(1S,3S)-3-((6-(5-(((bicyclo[1.1.1]pentan-1-ylcarbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (105),

(1S,3S)-3-((6-(5-(((1,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (Enantiomer A, 106)

(1S,3S)-3-((6-(5-(((1,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (Enantiomer B, 107),

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (108),

(1S,3S)-3-((6-(5-(((cyclopentylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (109),

(1S,3S)-3-((6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-(methyl-d3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (110),

(1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-(methyl-d3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (111),

(1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-(methyl-d3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (112),

- (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-(methyl-d3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (113), (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl-d3)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (114),
- 5 (3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic-1-d acid (115),
- (1S,3S)-3-((6-(5-(((isobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (116),
- (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((tetrahydro-2H-pyran-4-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-
- 10 carboxylic acid (117),
- (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyridin-2-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (118),
- 15 (1S,3S)-3-((6-(5-(((ethyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (119),
- (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyridin-3-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (120),
- 20 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyrimidin-2-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (121),
- (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyridin-4-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-
- 25 carboxylic acid (122),
- (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyrazin-2-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (123),
- (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((1-methyl-1H-pyrazol-5-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-
- 30 carboxylic acid (124),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(morpholin-3-ylmethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (125),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((tetrahydrofuran-3-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (126),

(1S,3S)-3-((6-(5-(((butyl(ethyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (127),

(1S,3S)-3-((6-(5-(((ethyl(propyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (128),

(1S,3S)-3-((6-(5-(((1-isopropylcyclopropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (129),

(1S,3S)-3-((6-(5-(((1-isobutylcyclopropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (130),

(1S,3S)-3-((6-(5-(((1-ethylcyclopropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (131),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-propylcyclobutyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (132),

(1S,3S)-3-((6-(5-(((1-ethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (133),

(1S,3S)-3-((6-(5-(((2-azaspiro[3.3]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (134),

(1S,3S)-3-((6-(5-(((6-azaspiro[3.4]octane-6-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (135),

(1S,3S)-3-((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (136),

(1S,3S)-3-((6-(5-(((3,3-dimethylpiperidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (137),

(1S,3S)-3-((6-(5-(((isopropyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (138),

(1S,3S)-3-((6-(5-(((3,3-difluorocyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid
5 (139),

(1S,3S)-3-((6-(5-(((3,3-dimethylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (140),

(1R,3S)-3-((6-(5-(((3,3-difluoro- cyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy) cyclohexane-1-carboxylic acid;
10 cis isomer from epimerization in final ester hydrolysis (141),

(1S,3S)-3-((6-(5-(((cyclopropyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (142),

(1S,3S)-3-((6-(5-(((3,3-difluoro- pyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (143),

(1S,3S)-3-((6-(5-(((5-azaspiro[2.4]heptane-5-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (144),

(1S,3S)-3-((6-(5-(((3,3-difluoro- cyclobutyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (145),

(1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(spiro[2.3]hexan-1-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (cis isomer from epimerization in final ester hydrolysis) (146),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-methylpyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (147),
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(1S,3S)-3-((6-(5-(((2-azabicyclo[2.2.1]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (148),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((octahydrocyclopenta[b]pyrrole-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (149),
30

(1S,3S)-3-((6-(5-(((3-(cyclopropylmethyl)pyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (150),

(1S,3S)-3-((6-(5-(((3-isobutylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (151),

(1S,3S)-3-((6-(5-(((2-ethylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (152),

(1S,3S)-3-((6-(5-(((2-isobutylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (153),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((2-(trifluoromethyl)pyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (154),

(1S,3S)-3-((6-(5-(((3,3-dimethylazetidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (155),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-methylazetidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (156),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((2-methylazetidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridine-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (157),

(1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(spiro[3.3]heptan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (158),

(1S,3S)-3-((6-(5-(((2-azaspiro[3.4]octane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (159),

(1R,3S)-3-((6-(5-(((3,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (cis isomer from epimerization in final ester hydrolysis step) (160),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-methylpiperidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (161),

(1S,3S)-3-((6-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (162),

(1S,3S)-3-((6-(5-(((3-isopropylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (163),

(1S,3S)-3-((6-(5-(((3-cyclopropylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (164),

(1S,3S)-3-((6-(5-(((3-ethylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (165),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-propylpyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (166),

(1S,3S)-3-((6-(5-(((7-azabicyclo [2.2.1]heptane-7-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (167),

(1S,3S)-3-((6-(5-(((3,3-dimethyl- cyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (168),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-phenylpyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (169),

(1S,3S)-3-((6-(5-(((tert-butyl (methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (170),

(1S,3S)-3-((6-(5-(((6-azaspiro [2.5]octane-6-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (171),

(1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(3-methylbut-2-en-1-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid (cis isomer from epimerization during final hydrolysis step) (172),

(1S,3S)-3-((6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (173),

(1S,3S)-3-((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (174),

(1S,3S)-3-((6-(5-(((6-azaspiro[3.4]octane-6-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid (175),

(1S,3S)-3-((6-(5-(((2-azaspiro[3.3]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid (176),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(3-methylbut-2-en-1-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid (177),

(1S,3S)-3-((6-(5-(((1-fluoro-2-methylpropan-2-yl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (178),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(spiro[2.3]hexan-5-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid (179),

(1S,3S)-3-((6-(1-methyl-5-(((methyl(spiro[3.3]heptan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy) cyclohexane-1-carboxylic acid (180),

(1S,3S)-3-((6-(5-(((3,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (181),

(1S,3S)-3-((6-(5-(((3-fluorocyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (182),

(1S,3S)-3-((6-(1-methyl-5-(((methyl(spiro[2.3]hexan-5-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (183),

(1S,3S)-3-((6-(5-((((2,2-dimethylcyclopropyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (184),

5 (1S,3S)-3-((6-(5-((((2,2-dimethylcyclopropyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (185),

(1S,3S)-3-((6-(5-((((2,2-difluorocyclopropyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers) (186),

(1S,3S)-3-((6-(5-((((3-fluoro-3-methylbutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (187),

(1S,3S)-3-((6-(5-((((3-fluoro-3-methylbutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (188),

(1S,3S)-3-((6-(5-((((1-fluorocyclobutyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (189),

(1S,3S)-3-((6-(5-((((3-fluoropropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (190),

(1S,3S)-3-((6-(5-((((4-fluorobutyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (191),

(1S,3S)-3-((6-(5-((((4-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (192),

25 (1R,3R)-3-((2-methyl-6-(1-methyl-5-((((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (193),

(1S,3S)-3-((6-(5-((((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (194),

30 (1S,3S)-3-((6-(5-((((cyclopentyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (195),

- (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (196),
- (1S,3S)-3-((2-ethyl-6-(5-(((isobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (197),
- 5 (1S,3S)-3-((6-(5-(((benzylcarbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (198),
- (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (199),
- (1S,3S)-3-((2-ethyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (200),
- 10 (1S,3S)-3-((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (201),
- (1S,3S)-3-((2-ethyl-6-(5-(((ethyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (202),
- 15 (1S,3S)-3-((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (203),
- (1S,3S)-3-((6-(5-(((3,3-dimethylazetidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (204),
- (1S,3S)-3-((6-(5-(((bicyclo[1.1.1]pentan-1-ylcarbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (205),
- 20 (1S,3S)-3-((6-(5-(((bicyclo[1.1.1]pentan-1-yl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (206),
- (1S,3S)-3-((2-ethyl-6-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (207),
- 25 (1S,3S)-3-((2-ethyl-6-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (208),
- (1S,3S)-3-((6-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (209),
- 30

- (1S,3S)-3-((6-(5-(((2-azaspiro[3.3]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (210),
- (1S,3S)-3-((6-(5-(((5-azaspiro[2.4]heptane-5-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (211),
- 5 (1S,3S)-3-((5-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (212),
- (1S,3S)-3-((5-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (213),
- (1S,3S)-3-((5-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (214),
- 10 (1S,3S)-3-((5-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (215),
- (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (216),
- 15 (1S,3S)-3-((5-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (219),
- (1S,3S)-3-((5-(5-(((cyclopropyl-methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (220),
- 20 (1S,3S)-3-((5-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (221),
- (1S,3S)-3-((5-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (222),
- (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(pentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (223),
- 25 (1S,3S)-3-((5-(5-(((isobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (224),
- (1S,3S)-3-((5-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (225),
- 30 (1S,3S)-3-((5-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (226),

(1S,3S)-3-((5-(5-(((cyclopentylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (227),

5 (1S,3S)-3-((5-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy) cyclohexane-1-carboxylic acid (228),

(1S,3S)-3-((5-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (229),

(1S,3S)-3-((5-(5-(((3-fluoropropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (230),

10 (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(neopentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (231),

(1S,3S)-3-((5-(5-(((2-fluoro-2-methylpropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (232),

15 (1S,3S)-3-((5-(5-(((1-fluoro-cyclobutyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (233),

(1S,3S)-3-((5-(5-(((1-fluorocyclopentyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (234),

20 (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(((1R,2R)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (235),

(1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(((1S,2S)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid (236),

(1S,3S)-3-((5-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid (237),

30 (1S,3S)-3-((5-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid (238),

(1S,3S)-3-((5-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid (239),

(1S,3S)-3-((5-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid (240),

(1S,3S)-3-((6-(5-(2-(((Cyclobutylmethyl)(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (241),

(1S,3S)-3-((2-Methyl-6-(1-methyl-5-(2-((methyl(propyl)carbamoyl)oxy)-ethyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt (242),

(1S,3S)-3-((6-(5-(2-((Cyclopentyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (243),

(1S,3S)-3-((6-(5-(2-((Benzyl(methyl)-carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (244),

(1S,3S)-3-((6-(5-(2-((Isobutyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (245),

(1S,3S)-3-((2-Methyl-6-(1-methyl-5-(2-((pyrrolidine-1-carbonyl)oxy)-ethyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt (246),

(1S,3S)-3-((6-(5-(2-(((Cyclobutyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt (247),

(1S,3S)-3-((6-(5-(2-(((Cyclobutyl-methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt (248),

(1S,3S)-3-((6-(5-(3-((Benzyl(methyl)carbamoyl)oxy)propyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (249),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(2-propoxyethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (250),

(1S,3S)-3-((6-(1-methyl-5-(((methyl(((1R,2R)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (251),

(1S,3S)-3-((6-(1-methyl-5-(((methyl(((1S,2S)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (252),

(1S,3S)-3-((6-(5-(((2-fluoro-2-methylpropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (253),

(1S,3S)-3-((5-(5-(((2-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid; mixture of diastereomers (254),

(1S,3S)-3-((6-(5-(((2-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid; mixture of diastereomers (255),

(1S,3S)-3-((6-(5-(((4-fluoropentyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (256),

(1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(((1R,2R)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (257),

(1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(((1S,2S)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (258),

(1S,3S)-3-((6-(5-(((2,2-difluoropropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (259),

(1S,3S)-3-((6-(5-(((3-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (260),

(1S,3S)-3-((6-(5-(((2-fluoropropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (261),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid; mixture of diastereomers (262),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((1-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (263),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(neopentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (264),

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(hydroxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (265),

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(fluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (266),

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (267),

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (268),

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (269),

(1S,3S)-3-((2-cyano-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (270),

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(2-hydroxypropan-2-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (271),

(1S,3S)-3-((2-Methoxy-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (272),

(1S,3S)-3-((6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (273),

(1S,3S)-3-((6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (274),

(1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (275),

5 (1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (276),

(1S,3S)-3-((2-(difluoromethyl)-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (277),

10 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (278),

(1S,3S)-3-((6-(5-(((cyclopropyl(methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (279),

15 (1S,3S)-3-((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (280),

(1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (281),

20 (1S,3S)-3-((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (282),

(1S,3S)-3-((2-(methoxymethyl)-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (283),

25 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (284),

30 (1S,3S)-3-((6-(5-(((cyclopropyl(methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (285),

(1S,3S)-3-((6-(5-(((cyclobutyl (methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (286),

5 (1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (287),

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl-d3)(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (288),

10 (1S,3S)-3-((2-cyano-6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (289),

(1S,3S)-3-((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-cyanopyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (290),

15 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-cyanopyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (291),

(1S,3S)-3-((2-cyano-6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (292),

(1S,3S)-3-((2-cyano-6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (293),

20 (1S,3S)-3-((2-cyano-6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (294).

In another embodiment, the compounds of the present invention have LPA1 IC₅₀ values ≤ 10 μM.

25 In another embodiment, the compounds of the present invention have LPA1 IC₅₀ values ≤ 1 μM.

In another embodiment, the compounds of the present invention have LPA1 IC₅₀ values ≤ 0.1 μM.

In another embodiment, the compounds of the present invention have LPA1 IC₅₀ values ≤ 0.05 μM.

30 In another embodiment, the compounds of the present invention have LPA1 IC₅₀ values ≤ 0.01 μM.

II. OTHER EMBODIMENTS OF THE INVENTION

In some embodiments, the compound of Formulas (I) – (IX), or a pharmaceutically acceptable salt thereof, is an antagonist of at least one LPA receptor. In some embodiments, the compound of Formulas (I)– (IX), or a pharmaceutically acceptable salt thereof, is an antagonist of LPA₁. In some embodiments, the compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is an antagonist of LPA₂. In some embodiments, the compound of Formulas (I) - (IX), 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, solvates or prodrugs of a compound of Formulas (I) - (IX).

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 and/or prophylaxis of a condition associated with LPA receptor mediated fibrosis, comprising administering to a patient in need of such treatment and/or prophylaxis 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.

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, "prophylaxis" is 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 prophylaxis therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. For prophylaxis treatment, conditions of the clinical disease state may or may not be presented yet. "Prophylaxis" 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

5 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

10 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

15 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

20 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,

25 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*

30 *Chemistry*, 68:2193-2222 (1996)).

The term "chiral" refers to the structural characteristic of a molecule that makes it

impossible to superimpose it on its mirror image. The term "homochiral" refers to a state

of enantiomeric purity. The term "optical activity" refers to the degree to which a homochiral molecule or nonracemic mixture of chiral molecules rotates a plane of polarized light.

As used herein, the term "alkyl" or "alkylene" is intended to include both
5 branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C₁ to C₁₀ alkyl" or "C₁₋₁₀ alkyl" (or alkylene), is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkyl groups. Additionally, for example, "C₁ to C₆ alkyl" or "C₁₋₆ alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced
10 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).

"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.

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"
30 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-.

"Halo" or "halogen" includes fluoro (F), chloro (Cl), bromo (Br), and iodo (I). "Haloalkyl" 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 halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

"Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C₁ to C₆ haloalkoxy" or "C₁₋₆ haloalkoxy", is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluoroethoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example, trifluoromethyl-S-, and pentafluoroethyl-S-.

The term "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".

As used herein, "carbocycle", "carbocyclyl" or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl,

adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and indanyl. When the term "carbocyclyl" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

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

"Aryl" groups refer to monocyclic or polycyclic aromatic hydrocarbons, including, for example, phenyl, naphthyl, 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). "C₆ or C₁₀ aryl" or "C₆₋₁₀ aryl" refers to phenyl and naphthyl. Unless otherwise specified, "aryl", "C₆ or C₁₀ aryl" or "C₆₋₁₀ aryl" or "aromatic residue" may be unsubstituted or substituted with 1 to 5 groups, preferably 1 to 3 groups, OH, OCH₃, Cl, F, Br, I, CN, NO₂, NH₂, N(CH₃)H, N(CH₃)₂, CF₃, OCF₃, C(=O)CH₃, SCH₃, S(=O)CH₃, S(=O)₂CH₃, CH₃, CH₂CH₃, CO₂H, and CO₂CH₃.

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

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic ring" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. 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 within the definition of the substitution of the heterocyclic ring). 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 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. When the term "heterocyclyl" is used, it is intended to include heteroaryl.

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

Examples of heterocycles include, but are not limited to, acridinyl, azetidiny, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiaziny, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidiny, imidazoliny, imidazolyl, 1H-indazolyl, imidazolopyridiny, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl,

isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, 5 oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-10 pyrrolidonyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinoliziny, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 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, 15 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, 20 oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benzotetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, 25 quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, 30 oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

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 the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

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

Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1H-indazolyl, benzimidazolyl, 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-quinoxalyl, and 1,2,3,4-tetrahydro-quinazolinyl.

As used herein, the term "aromatic heterocyclic group," "heteroaryl," or "heteroaryl ring" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. Heteroaryl groups can be substituted or unsubstituted. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent within the definition of the substitution of the heterocyclic ring). The nitrogen and sulfur

heteroatoms may optionally be oxidized (*i.e.*, N→O and S(O)_p) and the nitrogen atoms may optionally be quaternized.

Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane.

The term "counterion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

As referred to herein, the term "substituted" means that at least one hydrogen atom 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 keto (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Keto 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).

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 0-3 R groups,

then said group may optionally 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.

- 5 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
- 10 combinations result in stable compounds.

- 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
- 15 complication, commensurate with a reasonable benefit/risk ratio.

- 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. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts
- 20 of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts
- 25 prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

- The pharmaceutically acceptable salts of the present invention can be synthesized
- 30 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.

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

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

Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formulas (I)- (IX) compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formulas (I)- (IX) include C₁₋₆alkyl, C₁₋₆alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C₁₋₆ alkanoyloxy-C₁₋₆alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C₁₋₆alkoxycarbonyloxy-C₁₋₆alkyl (*e.g.*, methoxycarbonyloxy-methyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well-known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

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

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

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds have a variety of potential uses, e.g., as standards and reagents in determining the ability of a potential pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors *in vivo* or *in vitro*.

"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 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, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

5 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).

- 10 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.

- 15 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.

- 20 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
25 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
30 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-arachidonyl (20:4) LPA. Quantitatively minor alkyl LPA has biological activities similar to acyl LPA, and different LPA species activate LPA receptor subtypes with varied efficacies.

LPA RECEPTORS

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

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

LPA₂ (EDG-4) also couples with three types of G proteins, G_{i/o}, G_q, and G_{12/13}, to mediate LPA-induced cellular signaling. Expression of LPA₂ is observed in the testis, kidney, lung, thymus, spleen, and stomach of adult mice and in the human testis, pancreas, prostate, thymus, spleen, and peripheral blood leukocytes. Expression of LPA₂ is upregulated in various cancer cell lines, and several human LPA₂ transcriptional variants with mutations in the 3'-untranslated region have been observed. Targeted deletion of LPA₂ in mice has not shown any obvious phenotypic abnormalities, but has demonstrated a significant loss of normal LPA signaling (*e.g.*, PLC activation, Ca²⁺ mobilization, and stress fiber formation) in primary cultures of mouse embryonic fibroblasts (MEFs). Creation of *lpa1*(-/-) *lpa2* (-/-) double-null mice has revealed that many LPA-induced responses, which include cell proliferation, AC inhibition, PLC activation, Ca²⁺ mobilization, JNK and Akt activation, and stress fiber formation, are absent or severely reduced in double-null MEFs. All these responses, except for AC inhibition (AC inhibition is nearly abolished in LPA₁ (-/-) MEFs), are only partially affected in either LPA₁ (-/-) or LPA₂ (-/-) MEFs. LPA₂ contributes to normal LPA-mediated signaling responses in at least some cell types (Choi *et al*, *Biochemica et Biophysica Acta* 2008, 1781, p531-539).

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

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

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

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

Illustrative Biological Activity

15 Wound Healing

Normal wound healing occurs by a highly coordinated sequence of events in which cellular, soluble factors and matrix components act in concert to repair the injury. The healing response can be described as taking place in four broad, overlapping phases—hemostasis, inflammation, proliferation, and remodeling. Many growth factors
20 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
25 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
30 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

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

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

A number of muscular dystrophies are characterized by a progressive weakness and wasting of musculature, and by extensive fibrosis. It has been shown that LPA treatment of cultured myoblasts induced significant expression of connective tissue

growth factor (CTGF). CTGF subsequently induces collagen, fibronectin and integrin expression and induces dedifferentiation of these myoblasts. Treatment of a variety of cell types with LPA induces reproducible and high level induction of CTGF (J.P. Pradere, *et al.*, LPA₁ receptor activation promotes renal interstitial fibrosis, *J. Am. Soc. Nephrol.* 18 (2007) 3110–3118; N. Wiedmaier, *et al.*, *Int J Med Microbiol*; 298(3-4):231-43, 2008).
 5 CTGF is a profibrotic cytokine, signaling down-stream and in parallel with TGFβ.

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

10 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 fibrosis in humans (N. Watanabe, *et al.*, Plasma lysophosphatidic acid level and serum
 15 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,
 20 *Inhal. Toxicol.* 18 (2006) 389–393; K. Yasuda, *et al.*, *Lung* 172 (1994) 91–102).

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

25 **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.

30 LPA is an important mediator of fibroblast recruitment in pulmonary fibrosis. 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 in IPF. The end result is the aberrant healing process that characterizes this fibrotic condition.

5 The LPA₁ receptor is the LPA receptor most highly expressed on fibroblasts obtained from patients with IPF. Furthermore, BAL obtained from IPF patients induced chemotaxis of human foetal lung fibroblasts that was blocked by the dual LPA₁- LPA₃ receptor antagonist Ki16425. In an experimental bleomycin-induced lung injury mouse model, it was shown that LPA levels were high in bronchoalveolar lavage samples
10 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 samples compared with healthy controls. Increased fibroblast chemotactic activity in these samples was inhibited by the Ki16425 indicating that fibroblast migration is
15 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
20 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
25 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.

30

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 TGFβ. This induction was almost completely suppressed by co-treatment with the LPA-receptor antagonist Ki16425. In one aspect, the profibrotic activity of LPA in kidney results from a direct action of LPA on kidney cells involving induction of CTGF.

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
5 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
10 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
15 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 Formulas (I) - (IX), or a pharmaceutically
20 acceptable salt thereof, is used to treat or prevent fibrosis in a mammal. In one aspect, a compound of Formulas (I- (IX)), 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
25 compound of Formulas (I- (IX)), 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
30 of developing fibrosis of an organ or tissue. In one aspect, a compound of Formulas (I) - (IX), 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 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 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof: atherosclerosis, thrombosis, heart disease, vasculitis, formation of scar tissue, restenosis, phlebitis, COPD (chronic obstructive pulmonary disease), pulmonary hypertension, pulmonary fibrosis, pulmonary inflammation, bowel adhesions, bladder fibrosis and cystitis, fibrosis of the

nasal passages, sinusitis, inflammation mediated by neutrophils, and fibrosis mediated by fibroblasts.

In one aspect, a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is administered to a mammal with fibrosis of an organ or tissue or with a predisposition of developing fibrosis of an organ or tissue with one or more other agents that are used to treat fibrosis. In one aspect, the one or more agents include corticosteroids. In one aspect, the one or more agents include immunosuppressants. In one aspect, the one or more agents include B-cell antagonists. In one aspect, the one or more agents include uteroglobin.

In one aspect, a compound of Formulas (I) - (IX), 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 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is used to treat systemic sclerosis.

Pain

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 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 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).

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

Cancer

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

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

LPA contributes to tumorigenesis by increasing motility and invasiveness of cells. LPA has been implicated in the initiation or progression of ovarian cancer. LPA is present at significant concentrations (2–80 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
5 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
10 cancer progression, drug resistance, and prognosis in ovarian cancer. In some embodiments, a compound of Formulas (I) - (IX) inhibits or reduces IL-8 expression in ovarian cancer cell lines.

In one aspect, a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is used in the treatment of cancer. In one aspect, a compound of
15 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is used in the treatment of malignant and benign proliferative disease. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt 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
20 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, and a second therapeutic agent, wherein the second therapeutic agent is an anti-cancer agent.

25 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
30 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),

5 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, ependyoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer,

10 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

15 histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenström macroglobulinemia, medulloblastoma, medulloepithelioma,

20 melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer,

25 papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary

30 gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sézary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive

neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, Wilms tumor.

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

Respiratory and Allergic Disorders

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

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

In one aspect, in the asthmatic individual, the release of normal repair mediators, including LPA, is exaggerated or the actions of the repair mediators are inappropriately prolonged leading to inappropriate airway remodeling. Major structural features of the

remodeled airway observed in asthma include a thickened lamina reticularis (the basement membrane-like structure just beneath the airway epithelial cells), increased numbers and activation of myofibroblasts, thickening of the smooth muscle layer, increased numbers of mucus glands and mucus secretions, and alterations in the
5 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
10 hyperresponsiveness of the asthmatic airway. In one aspect, LPA contributes to the hyperresponsiveness that is a primary feature of acute exacerbations of asthma.

In addition to the cellular responses mediated by LPA, several of the LPA signaling pathway components leading to these responses are relevant to asthma. EGF receptor upregulation is induced by LPA and is also seen in asthmatic airways (M. Amishima, *et al.*, *Am. J. Respir. Crit. Care Med.* 157, 1907–1912, 1998). Chronic
15 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
20 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
25 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,
30 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is used in the treatment of various allergic disorders in a mammal. In one aspect, a compound of Formulas (I) - (IX), 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is used in the treatment of asthma in a mammal. In one aspect, a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is used in the treatment of chronic asthma in a mammal.

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

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

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

Nervous System

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

15 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,
20 1995). Immortalized CNS neuroblast cell lines from the cerebral cortex also display retraction responses to LPA exposure through Rho activation and actomyosin interactions. In one aspect, LPA is associated with post-ischemic neural damage (*J. Neurochem.* 61, 340, 1993; *J. Neurochem.*, 70:66, 1998).

In one aspect, provided is a compound of Formulas (I) - (IX), or a
25 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,
30 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a CNS disorder in a mammal. CNS disorders include, but are not limited to, multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke, cerebral ischemia, retinal ischemia, post-surgical cognitive dysfunction, migraine, peripheral neuropathy/neuropathic pain, spinal cord injury, cerebral edema and head injury.

Cardiovascular Disorders

Cardiovascular phenotypes observed after targeted deletion of lysophospholipid 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
5 receptor antagonists that prevent thrombus and neointima plaque formation.

In one aspect, a compound of Formulas (I) - (IX), 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
10 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
15 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
20 to the mammal an effective amount of at least one compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, or pharmaceutical composition or medicament which includes a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

In one aspect, provided herein are methods for reducing cardiac reperfusion injury
25 following myocardial ischemia and/or endotoxic shock comprising administering at least once to the mammal an effective amount of at least one compound of Formulas (I) - (IX), 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
30 amount of at least one compound of Formulas (I) - (IX), 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

5

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 Formulas (I) - (IX), 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 Formulas (I) - (IX), 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 Formulas (I) - (IX), 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.

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 Formulas (I) - (IX), 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 indirectly modulated, including reducing and/or inhibiting, by the administration of (at least once) a therapeutically effective amount of at least one compound of Formulas (I) - (IX), 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.

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).

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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

In certain aspects, are methods for the treatment of cystitis, including, *e.g.*, interstitial cystitis, comprising administering at least once to the mammal a

therapeutically effective amount of at least one compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

In accordance with one aspect, methods described herein include the diagnosis or determination of whether or not a patient is suffering from a LPA-dependent or LPA-mediated disease or condition by administering to the subject a therapeutically effective amount of a compound of Formulas (I) - (IX), 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 Formulas (I) - (IX), pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, which are antagonists of LPA₁, and are used to treat patients suffering from one or more LPA-dependent or LPA-mediated conditions or diseases, including, but not limited to, lung fibrosis, kidney fibrosis, liver fibrosis, scarring, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, arthritis, allergy, psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, pain, proliferative disorders and inflammatory conditions. In some embodiments, LPA-dependent conditions or diseases include those wherein an absolute or relative excess of LPA is present and/or observed.

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

In one aspect, a compound of Formulas (I) - (IX), or a pharmaceutically 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 Formulas (I)- (IX), 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

In one aspect, presented herein is the use of a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of Sjogren
5 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 Formulas (I) - (IX), 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
10 one aspect, presented herein is the use of a compound of Formula (I), 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 Formulas (I) - (IX), 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 Formulas (I) - (IX), 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
20 compound of Formulas (I) - (IX), 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, in the promotion of adipose tissue formation in a mammal comprising administering at least
25 once to the mammal an effective amount of at least one compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

a. In Vitro Assays

The effectiveness of compounds of the present invention as LPA₁ inhibitors can
30 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 µM. and were then incubated for 20 min at room temperature at which time LPA (Avanti Polar Lipids Cat#857130C) was added at final concentrations of 10 nM to stimulate the cells. 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).

15

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 µg/µL). Exactly 2 minutes following the LPA challenge, the mice are euthanized by decapitation and the trunk blood is collected. These samples are collectively centrifuged and individual 75 µL samples are frozen at -20°C until the time of the histamine assay.

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

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 µg/µL. 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.

30

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

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

In some embodiments, the pharmaceutical composition further comprises one or 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-
 5 151, 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. In some embodiments, provided is a method comprising administering a compound of
 10 Formulas (I) - (IX), 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof. In some embodiments, the method further comprises administering one or more additional
 15 therapeutically active agents other than a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

In some embodiments, the one or more additional therapeutically active agents other than a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, are selected from: corticosteroids (e.g., dexamethasone or fluticasone),
 20 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, autotaxin inhibitors,
 25 decongestants, antihistamines (e.g., loratidine), mucolytics, anticholinergics, antitussives, expectorants, anti-infectives (e.g., fusidic acid, particularly for treatment of atopic dermatitis), anti-fungals (e.g., clotriazole, particularly for atopic dermatitis), anti-IgE antibody therapies (e.g., omalizumab), β -2 adrenergic agonists (e.g., albuterol or salmeterol), other PGD₂ antagonists acting at other receptors such as DP antagonists,
 30 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 one or more additional therapeutically active agents other than a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, are other anti-fibrotic agents selected from pirfenidone, nintedanib, thalidomide, 5 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, 10 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, are selected from ACE inhibitors, ramipril, AII antagonists, irbesartan, anti- 15 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 20 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, 25 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 Formulas (I) - (IX), or a pharmaceutically acceptable salt 30 thereof, are selected from Gremlin-1 mAb, PAI-1 mAb, Promedior (PRM-151; recombinant human Pentraxin-2); FGF21, TGF β antagonists, α v β 6 & α v β pan-

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

Pharmaceutical formulations described herein are administrable to a subject in a variety of ways by multiple administration routes, including but not limited to, oral, 5 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, 10 capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

In some embodiments, the compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is administered orally.

15 In some embodiments, the compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is administered topically. In such embodiments, the compound of Formulas (I) - (IX), 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, 20 balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. In one aspect, the compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is administered topically to the skin.

In another aspect, the compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is administered by inhalation. In one embodiment, the compound 25 of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is administered by inhalation that directly targets the pulmonary system.

In another aspect, the compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof, is formulated for intranasal administration. Such formulations 30 include nasal sprays, nasal mists, and the like.

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

In another aspect is the use of a compound of Formulas (I) - (IX), 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 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 Formulas (I) - (IX), 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 Formulas (I) - (IX) 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 of a compound of Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof.

In some cases disclosed herein is the use of a compound of Formulas (I) - (IX), 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 Formulas (I) - (IX), 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 Formulas (I) - (IX), or a pharmaceutically 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 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 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 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 Formulas (I) - (IX) 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 Formula (I), 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,
5 occupational/environmental (Farmer lung), granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease (scleroderma and others), alveolar proteinosis, langerhans cell granulomatosis, lymphangioleiomyomatosis, Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease.

10 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.

15 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
20 mammal: tubulointerstitium fibrosis, glomerular sclerosis.

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 Formulas (I) - (IX), or a pharmaceutically acceptable salt thereof. In various
25 embodiments, each agent is administered in any order, including simultaneously.

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

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

In some embodiments, compounds provided herein are orally administered.

In some embodiments, compounds provided herein are used as antagonists of at
30 least one LPA receptor. In some embodiments, compounds provided herein are used for inhibiting the activity of at least one LPA receptor or for the treatment of a disease or

condition that would benefit from inhibition of the activity of at least one LPA receptor. 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.

5 Articles of manufacture, which include packaging material, a compound of Formulas (I) - (IX), 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
10 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.

15

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
20 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
25 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
30 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)).

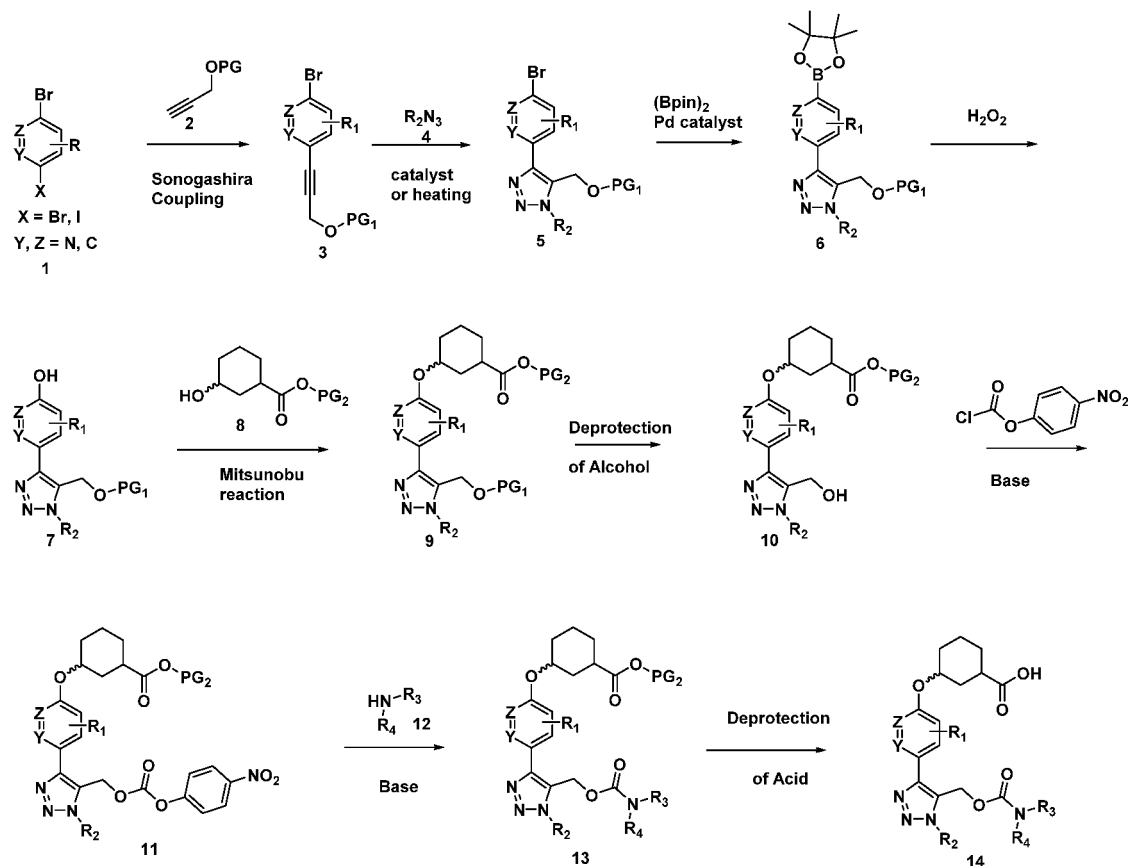
The compounds of Formulas (I) - (IX) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear herein after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

Scheme 1 describes the synthesis of carbamoyloxymethyl triazole-aryloxy cyclohexyl acids 14. A dihalo (preferably dibromo) phenyl or azine (e.g. pyridine) derivative 1 is coupled with an appropriately protected (e.g. as a tetrahydropyranyl ether) propargyl alcohol 2 under Sonogashira conditions (e.g. Alper, P. et al, WO 2008097428) to give the corresponding bromo-aryl or bromo-heteroaryl protected propargyl alcohol 3. Thermal reaction of alkyne 3 with an alkyl azide 4 (with or without an appropriate catalyst; Qian, Y. et al, *J. Med. Chem.*, **2012**, 55, 7920-7939 or Boren, B. C., et al., *J. Am. Chem. Soc.*, **2008**, 130, 8923-8930) provides the corresponding regioisomeric protected hydroxymethyl- triazoles, from which the desired triazole regioisomer 5 can be isolated. Reaction of the bromoaryl- or bromoheteroaryl-triazoles 5 with pinacol diboronate in the presence of an appropriate palladium catalyst (Ishiyama, T. et al, *J. Org. Chem.* **1995**, 60, 7508-7510) provides the corresponding pinacol boronate 6, which is then oxidized with hydrogen peroxide to give the corresponding phenol or hydroxyheteroarene 7 (Fukumoto, S. et al, WO 2012137982). Reaction of

phenol/hydroxyheteroarene 7 with a 3-hydroxy cycloalkyl ester 8 under Mitsunobu reaction conditions (Kumara Swamy, K. C., *Chem. Rev.*, **2009**, *109*, 2551-2651) furnishes the corresponding triazole cycloalkyl ether ester 9. Deprotection of the hydroxytriazole 9 provides the triazole alcohol 10, which is then reacted with 4-nitrophenyl chloroformate
5 in the presence of an appropriate base to give the corresponding triazole 4-nitrophenyl carbonate 11. The triazole 4-nitrophenyl carbonate 11 is then reacted with an amine 12 in the presence of an appropriate base to give the triazole carbamate 13, which then undergoes ester deprotection to give the desired carbamoyloxymethyltriazole-aryloxy cycloalkyl acids 14.

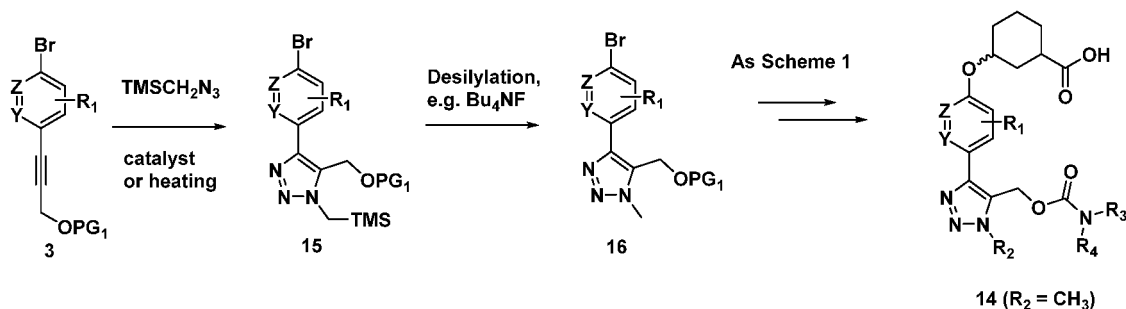
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Scheme 1.



For the specific example of analogs 14, where $\text{R}_2 = \text{CH}_3$ (Scheme 1A), instead of using an alkyl azide for the cycloaddition to the protected hydroxyalkyl alkyne 3, trimethylsilyl azide is a viable replacement reagent (Qian, Y. et al, *J. Med. Chem.*, **2012**, 55, 7920-7939) that can be used under either thermal or transition-metal catalyzed conditions (Boren, B.C. et. al., *J. Am. Chem. Soc.*, **2008**, 130, 8923-8930). Under these conditions, the desired triazole regioisomer 15 is obtained as the major product of the 1,3-dipolar cycloaddition reaction, and the trimethylsilyl group is subsequently removed under standard desilylation conditions (*e.g.* Bu_4NF , as in Qian, Y. et al, *J. Med. Chem.*, **2012**, 55, 7920-7939).

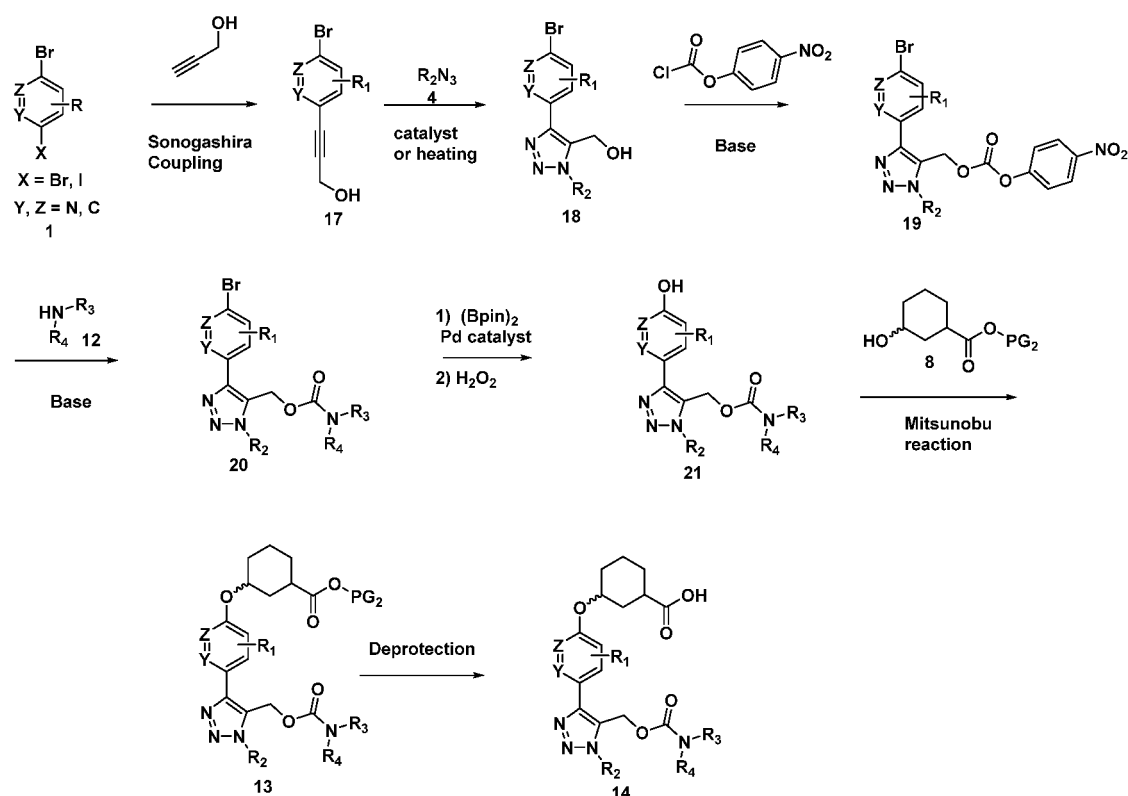
Scheme 1A.



5 Scheme 2 describes an alternative synthetic route to the carbamoyloxymethyl triazole-aryloxy cyclohexyl acids 14. A dihalo (preferably dibromo) phenyl or azine (e.g. pyridine) derivative 1 is coupled with propargyl alcohol under Sonogashira conditions (Alper, P. et al, WO 2008097428) to give the corresponding bromo-aryl or bromo-heteroaryl propargyl alcohol 3. Thermal reaction of alkyne 3 with an alkyl azide 4 (with or without an appropriate catalyst, Qian, Y. et al, *J. Med. Chem.*, **2012**, 55, 7920-7939; Boren, B.C. et. al., *J. Am. Chem. Soc.*, **2008**, 130, 8923-8930) provides the corresponding regioisomeric hydroxymethyl-triazoles, from which the desired triazole regioisomer 18 can be isolated. Triazole alcohol 18 is then reacted with 4-nitrophenyl chloroformate in the presence of an appropriate base to give the corresponding triazole 4-nitrophenyl carbonate 19, which is then reacted with an amine 12 in the presence of an appropriate base to give the aryl/heteroaryl-triazole carbamate 20. The bromo-aryl/heteroaryl triazole 20 is then converted to the hydroxyaryl or hydroxy-heteroaryl triazole 21 via the corresponding boronate using the 2 step sequence [B(pin)]₂/Pd-catalysis followed by treatment with H₂O₂] described in Scheme 1. Hydroxyaryl/heteroaryl triazole 22 is then reacted with a 3-hydroxy cycloalkylester 8 under Mitsunobu reaction conditions (Kumara Swamy, K. C., *Chem. Rev.*, **2009**, 109, 2551-2651) to furnish the corresponding triazole cycloalkyl ether ester 13 which is then deprotected to give the desired carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 14.

25

Scheme 2.



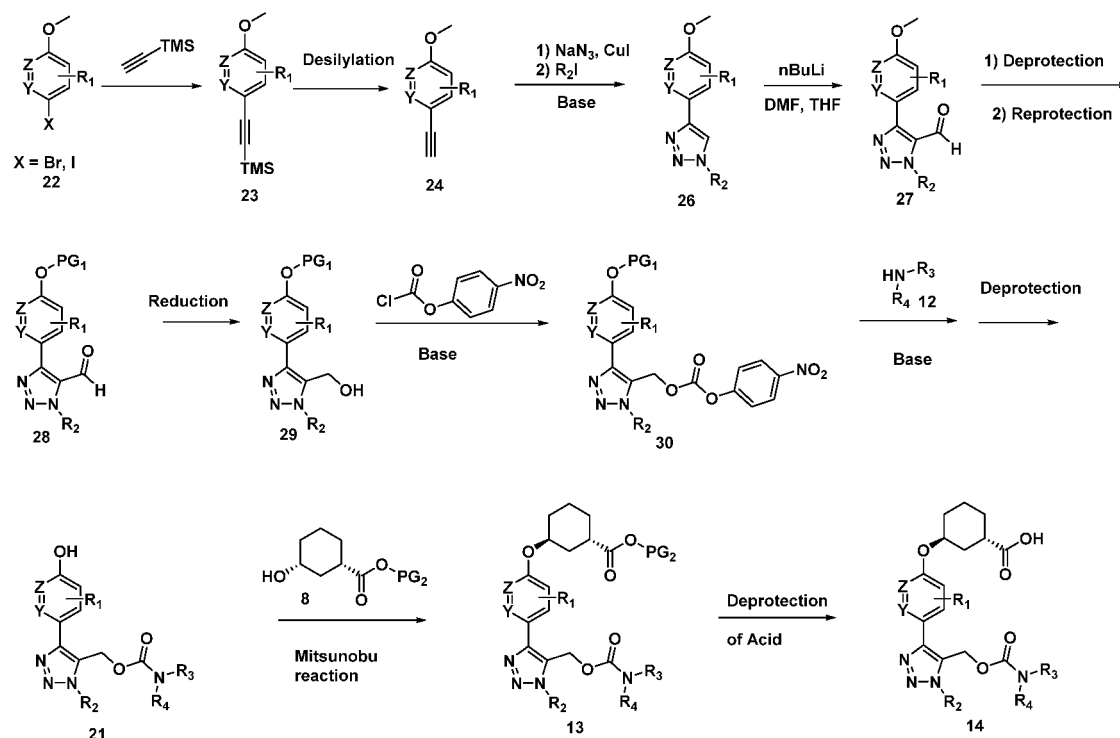
- Another alternative synthesis of carbamoyloxymethyl triazole-aryloxy cyclohexyl acids 14 is described in Scheme 3. Reaction of an alkoxyphenyl or azine (*e.g.* pyridine) derivative 1 with trimethylsilyl acetylene under Sonogashira conditions (Alper, P. et al, WO 2008097428) gives the corresponding alkoxy-aryl or heteroaryl silyl acetylene 23, which is then desilylated under standard conditions (*e.g.* Bu_4NF) to give the alkyne 24. Thermal reaction of alkyne 24 with sodium azide gives the corresponding triazole (Roehrig, U. et al, WO 2009127669), which is then alkylated with an alkyl iodide 25 under basic conditions to give a mixture of regioisomeric alkylated triazoles, from which the desired triazole regioisomer 26 can be isolated. Lithiation of triazole 26 (Hernandez, M. et al, US 20120115844) followed by reaction with a formylating agent, *e.g.* dimethyl formamide, provided the triazole aldehyde 27. Deprotection of the alkoxy group of arene/heteroarene 27 followed by re protection of the phenol/hydroxy-heteroarene with a more labile protecting group (*e.g.* *t*-butyldimethylsilyl ether) gives the protected aryl/heteroaryl triazole aldehyde 28, which is then reduced by standard methods (*e.g.* NaBH_4) to the corresponding triazole alcohol 29. Triazole alcohol 29 is reacted with 4-

nitrophenyl chloroformate to give the corresponding triazole 4-nitrophenyl carbonate 30.

This triazole carbonate 30 is then reacted with an amine 12 in the presence of an appropriate base to give the corresponding triazole carbamate, which subsequently undergoes deprotection to provide the hydroxy aryl/hetero-aryl triazole carbamate 21.

- 5 The hydroxy aryl/heteroaryl triazole carbamate 21 then is subjected to a Mitsunobu reaction with 3-hydroxy cycloalkyl ester 8 to furnish the corresponding triazole cycloalkyl ether ester 13, followed by ester deprotection to give the desired carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 14.

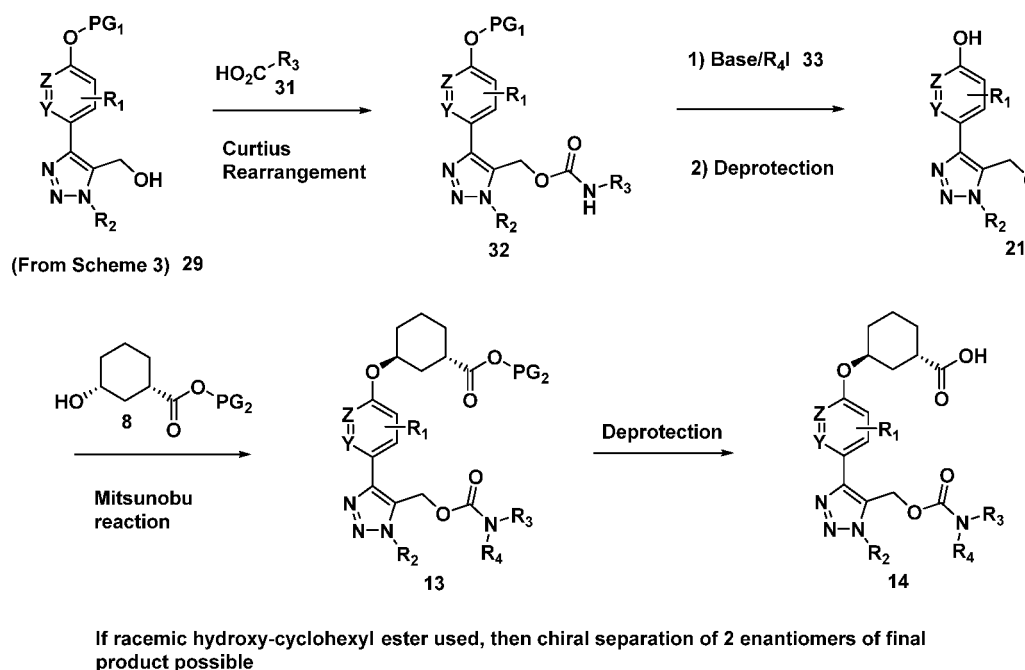
10 Scheme 3.



- 15 A different synthetic route for the preparation of triazole carbamate acids 14 is described in Scheme 4. The protected hydroxyaryl/heteroaryl triazole alcohol 29 is reacted with the intermediate isocyanate generated from a carboxylic acid 31 under Curtius reaction conditions (Seiders, T. et al, WO 2011041694A2) to give the monoalkyl NH-carbamate 32. Base-mediated reaction of NH-carbamate 32 with an appropriate alkyl iodide 33 provides the corresponding triazole N-disubstituted carbamate, which is then

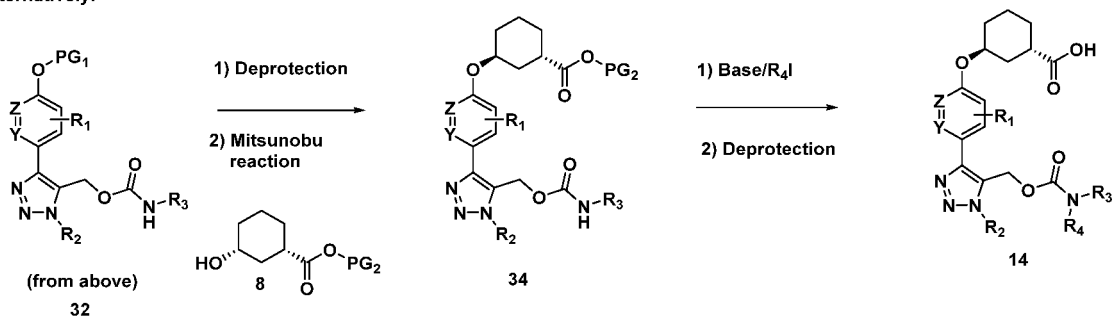
deprotected to provide the hydroxy aryl/heteroaryl triazole carbamate 21. Hydroxy aryl/heteroaryl triazole carbamate 21 then is subjected to a Mitsunobu reaction with 3-hydroxy cycloalkylester 8 to furnish the corresponding triazole cycloalkyl ether ester 13 followed by ester deprotection to give the desired carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 14. Alternatively, the triazole monoalkyl NH-carbamate 32 is deprotected to give the hydroxy aryl/heteroaryl triazole carbamate, which is then reacted with 3-hydroxy cycloalkylester 8 under Mitsunobu reaction conditions to provide the triazole-aryloxy cyclohexyl ester NH-carbamate 34. Intermediate NH-carbamate 34 is then alkylated with alkyl iodide 33 under basic conditions; subsequent ester deprotection furnishes the desired carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 14.

Scheme 4.



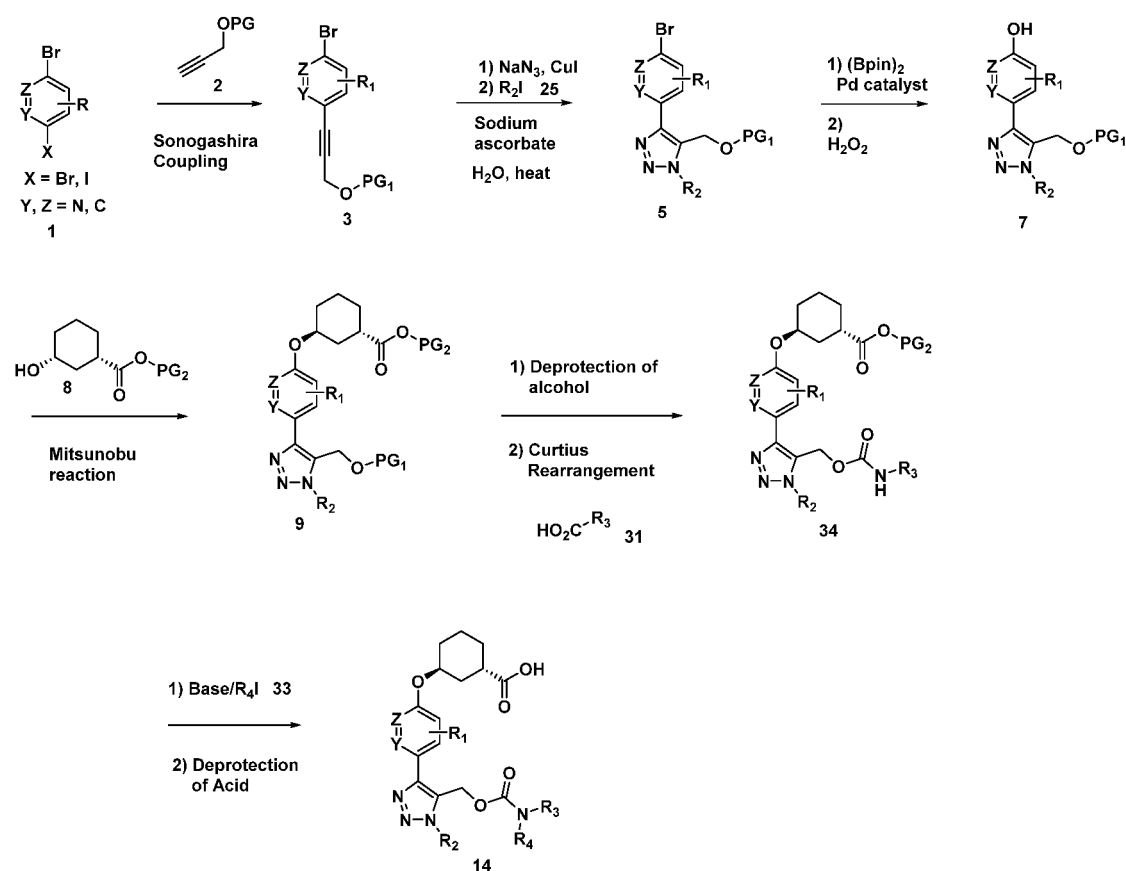
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Alternatively:



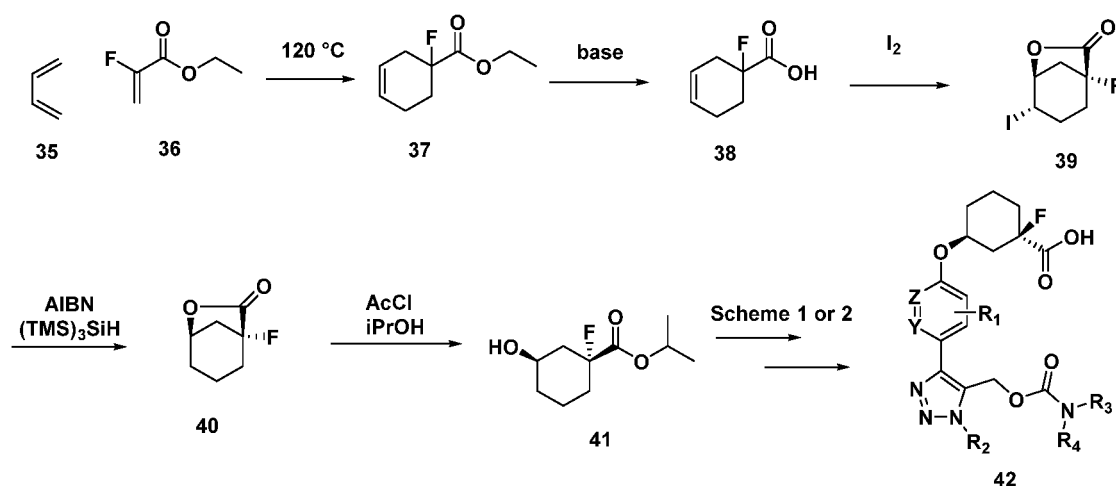
An alternative synthesis of carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 14 from the protected hydroxyalkyltriazole cycloalkyl ether ester 9 is described in Scheme 5. Selective deprotection of the alcohol of 9 followed by its reaction with the isocyanate generated from the Curtius rearrangement of an alkyl carboxylic acid 31 provides the triazole NH monoalkyl carbamate 34. The triazole NH-carbamate 34 is then alkylated with alkyl iodide 33 under basic conditions, followed by ester deprotection to give the desired carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 14.

Scheme 5.



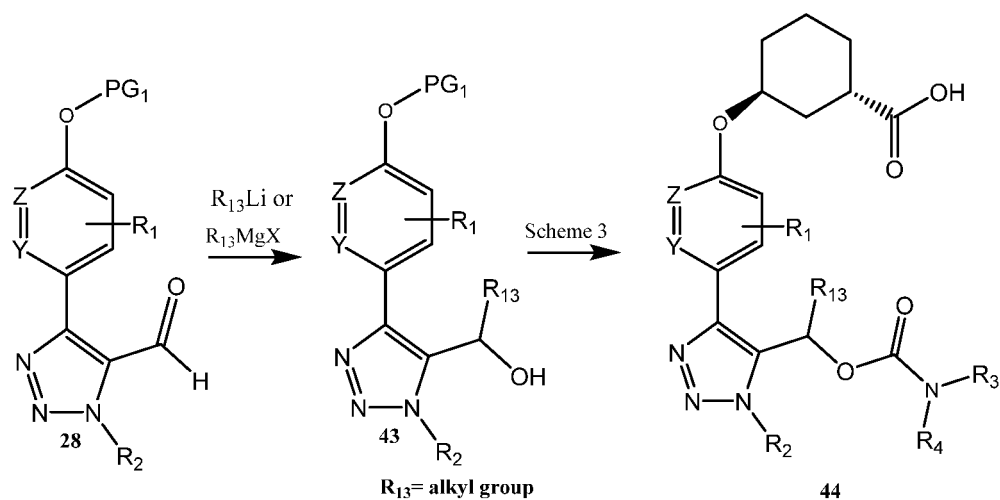
Scheme 6 describes the synthesis of carbamoyloxy methyltriazole-aryloxy α -F
 cyclohexyl acids **42**. Diels-Alder reaction of diene **35** and ethyl 2-fluoroacrylate **36** under
 thermal conditions (e.g. procedure of Kotikyan et al., *Bulletin of the Academy of Sciences
 of the USSR, Division of Chemical Science (Engl.)*, **1971**, 20, 292) gives the α -F
 cyclohexyl ester **37**. Hydrolysis of ester **37** under basic condition provides acid **38**.
 Iodolactonization (e.g. Nolsee, J. M. J. et al., *Eur. J. Org. Chem.*, **2014**, 3051-3065) of the
 olefin with the carboxylic acid of **38** gives iodolactone **39**. Deiodination under radical
 condition (e.g. AIBN/ $(\text{TMS})_3\text{SiH}$, ref. Chatgililoglu, C. et al., *Molecules*, **2012**, 17, 527-
 555) affords lactone **40**. Opening of lactone **40** via acidic condition (e.g. AcCl in $i\text{PrOH}$)
 gives the α -F cyclohexyl ester **41**. The carbamoyloxy methyltriazole-aryloxy α -F
 cyclohexyl acids **42** are synthesized from the α -F cyclohexyl ester **41** following the
 general synthetic procedure described in Schemes 1 or 2.

Scheme 6.



Scheme 7 describes the synthesis of carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 44. Addition of an alkyl organometallic reagent (e.g. $R_{13}Li$ or $R_{13}MgX$) to aldehyde 28 gives triazole alcohol 43. The carbamoyloxy methyltriazole-aryloxy cyclohexyl acids 44 can then be synthesized from triazole alcohol 43 following the general synthetic procedure described in Scheme 3.

Scheme 7.



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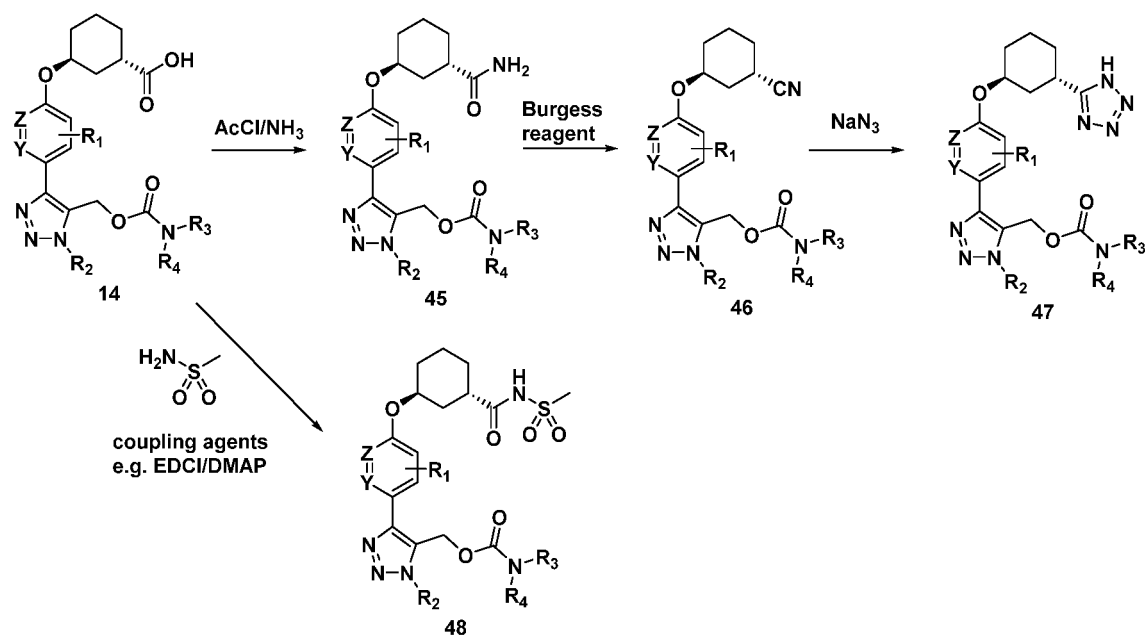
Scheme 8 describes the synthesis of carbamoyloxy methyltriazole-aryloxy cyclohexyl amides 45, tetrazoles 47 and acyl sulfonamide 48. Treatment of acid 14 with $AcCl$ followed by ammonia gives primary amide 45. Dehydration of primary amide 45 with Burgess reagent (Talibi, P. et al., *e-EROS Encyclopedia of Reagents for Organic Synthesis*, published online 15 Sept. 2008, DOI: 10.1002/047084289X.rm095m.pub2)

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furnishes nitrile 46. Cycloaddition of azide to nitrile 46 affords the tetrazole 47. In a similar manner to the preparation of amides 45, acyl sulfonamides 48 can be synthesized by the reaction of carboxylic acid 14 with methyl sulfonamide using standard coupling agents (e.g. EDC/DMAP).

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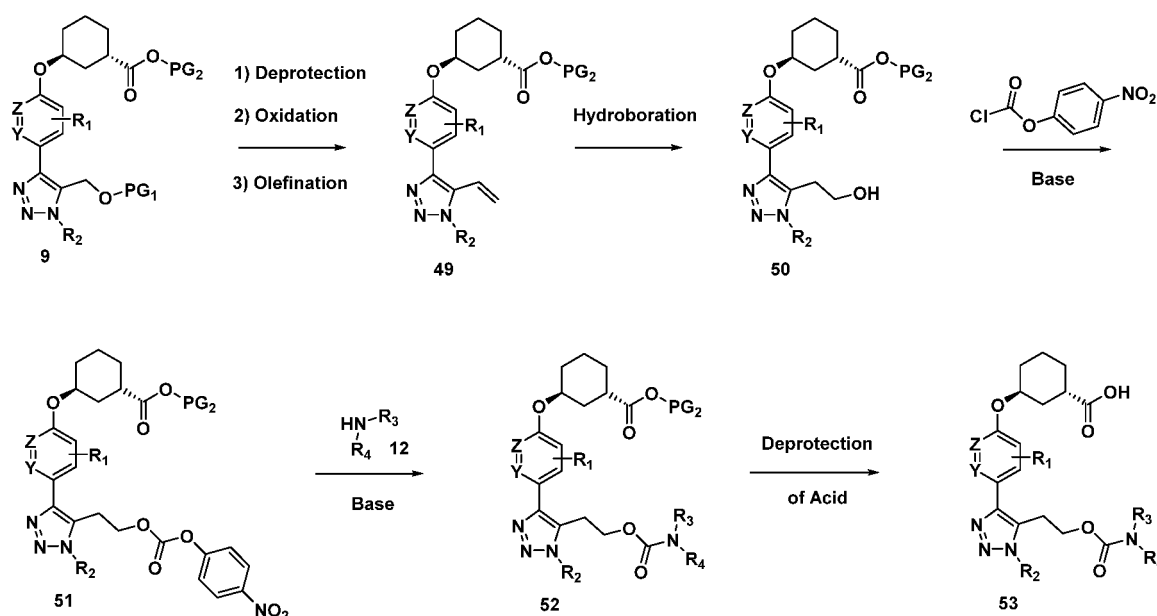
Scheme 8



Scheme 9 describes the synthesis of carbamoyloxyethyl triazole-aryloxy cyclohexyl acids 53. The protected alcohol intermediate 9 is deprotected to the corresponding alcohol, which is then oxidized to the corresponding aldehyde (e.g. Dess-Martin periodinane or Swern oxidation) which is then subjected to an olefination reaction (e.g. Wittig or Peterson olefination reaction) which provides the terminal olefin 49. Hydroboration of olefin 49 at the terminal carbon (e.g. with 9-BBN), followed by oxidative workup, provides the corresponding triazole ethyl alcohol 50. Triazole ethyl alcohol 50 is reacted with 4-nitrophenyl chloroformate in the presence of an appropriate base to give the corresponding triazole 4-nitrophenyl carbonate 51. The triazole 4-nitrophenyl carbonate 51 is then reacted with an amine 12 in the presence of an appropriate base to give the triazole carbamate 52, which then undergoes ester deprotection to give the desired carbamoyloxyethyltriazole-aryloxy cycloalkyl acids 53.

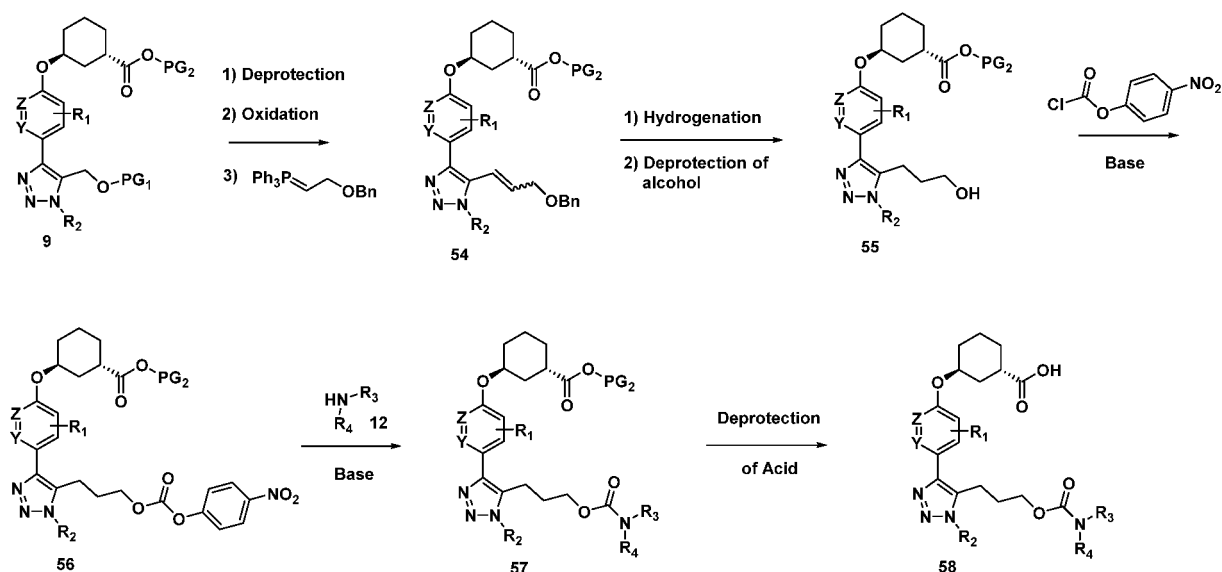
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Scheme 9.



Scheme 10 describes the synthesis of carbamoyloxypropyl triazole-aryloxy
 cyclohexyl acids 58. The protected alcohol intermediate 9 is deprotected to the
 5 corresponding alcohol, then is oxidized to the corresponding aldehyde which is then
 subjected to olefination conditions (eg. Wittig reaction with a reagent with an
 appropriately protected alcohol such as 2-(benzyloxy) ethylidene) as shown) which
 provides olefin 54 as a mixture of *cis/trans* isomers. Hydrogenation of the olefin,
 followed by deprotection of the alcohol (e.g. using hydrogenolysis with H₂), provides the
 10 corresponding triazole alcohol 55. The triazole alcohol 55 is reacted with 4-nitrophenyl
 chloroformate in the presence of an appropriate base to give the corresponding triazole 4-
 nitrophenyl carbonate 56. The triazole 4-nitrophenyl carbonate 56 is then reacted with an
 amine 12 in the presence of an appropriate base to give the triazole carbamate 57, which
 then undergoes ester deprotection to give the desired carbamoyloxypropyltriazole-aryloxy
 15 cycloalkyl acids 58.

Scheme 10.



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 spectrometry, "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> -butoxycarbonyl
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
AcOH or HOAc	acetic acid
AlCl ₃	aluminum trichloride
AIBN	Azobis-isobutyronitrile
BBR ₃	boron tribromide
BCl ₃	boron trichloride
BEMP	2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BOP reagent	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Burgess reagent	1-methoxy-N-triethylammoniosulfonyl-methanimidate
CBz	carbobenzyloxy
DCM or CH ₂ Cl ₂	dichloromethane
CH ₃ CN or ACN	acetonitrile
CDCl ₃	deutero-chloroform
CHCl ₃	chloroform
mCPBA or m-CPBA	<i>meta</i> -chloroperbenzoic acid
Cs ₂ CO ₃	cesium carbonate
Cu(OAc) ₂	copper (II) acetate
Cy ₂ NMe	N-cyclohexyl-N-methylcyclohexanamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2 dichloroethane
DEA	diethylamine

Dess-Martin	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one
DIC or DIPCDI	diisopropylcarbodiimide
DIEA, DIPEA or 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-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
(<i>S,S</i>)-EtDuPhosRh(I)	(+)-1,2-bis((2 <i>S</i> ,5 <i>S</i>)-2,5-diethylphospholano)benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate
Et ₃ N or TEA	triethylamine
EtOAc	ethyl acetate
Et ₂ O	diethyl ether
EtOH	ethanol
GMF	glass microfiber filter
Grubbs II	(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium
HCl	hydrochloric acid
HATU	O-(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
Hex	hexane
HOBt or HOBt	1-hydroxybenzotriazole
H ₂ O ₂	hydrogen peroxide
IBX	2-iodoxybenzoic acid
H ₂ SO ₄	sulfuric acid

Jones reagent	CrO ₃ in aqueous H ₂ SO ₄ , 2 M solution
K ₂ CO ₃	potassium carbonate
K ₂ HPO ₄	potassium phosphate dibasic (potassium hydrogen phosphate)
KOAc	potassium acetate
K ₃ PO ₄	potassium phosphate tribasic
LAH	lithium aluminum hydride
LG	leaving group
LiOH	lithium hydroxide
MeOH	methanol
MgSO ₄	magnesium sulfate
MsOH or MSA	methylsulfonic acid/methanesulfonic acid
NaCl	sodium chloride
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
Na ₂ CO ₃	sodium carbonate
NaOH	sodium hydroxide
Na ₂ SO ₃	sodium sulfite
Na ₂ SO ₄	sodium sulfate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NH ₃	ammonia
NH ₄ Cl	ammonium chloride
NH ₄ OH	ammonium hydroxide
NH ₄ ⁺ HCO ₂ ⁻	ammonium formate
NMM	N-methylmorpholine
OTf	triflate or trifluoromethanesulfonate
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
Pd(OAc) ₂	palladium(II) acetate
Pd/C	palladium on carbon
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)
Ph ₃ PCl ₂	triphenylphosphine dichloride
PG	protecting group

POCl ₃	phosphorus oxychloride
PPTS	pyridinium p-toluenesulfonate
i-PrOH or IPA	isopropanol
PS	Polystyrene
RT or rt	room temperature
SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
SiO ₂	silica oxide
SnCl ₂	tin(II) chloride
TBAF	tra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMSCHN ₂	Trimethylsilyldiazomethane
TMSCH ₂ N ₃	Trimethylsilylmethyl azide
T3P	propane phosphonic acid anhydride
TRIS	tris (hydroxymethyl) aminomethane
pTsOH	p-toluenesulfonic acid

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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;

15 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.

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

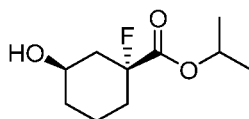
20 Mobile Phase A: 5:95 CH₃CN:water with 0.1% TFA;

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

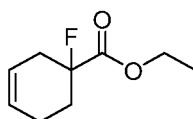
Temperature: 50 °C; Gradient: 0-100% B over 3 min, then a 0.75-min hold at 100%

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

25 Intermediate 1 (±)-cis-isopropyl 1-fluoro-3-hydroxycyclohexanecarboxylate

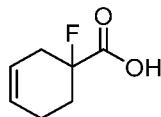


Intermediate 1A (±)-ethyl 1-fluorocyclohex-3-enecarboxylate



A mixture of 20% buta-1,3-diene in toluene (13.8 mL, 41.1 mmol) and ethyl 2-fluoroacrylate (3.07 mL, 27.4 mmol) was heated at 120 °C in a sealed tube for 7 days. The reaction was cooled to rt and concentrated *in vacuo*. The residue was chromatographed (80 g SiO₂) with EtOAc/Hexane (continuous gradient from 0% to 10% EtOAc over 20 min) to give Intermediate 1A (3.80 g, 22.1 mmol, 80 % yield) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 5.79 (ddd, *J*=9.9, 4.7, 2.2 Hz, 1H), 5.64 - 5.58 (m, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 2.73 - 2.57 (m, 1H), 2.45 - 2.23 (m, 2H), 2.20 - 1.91 (m, 3H), 1.32 (t, *J*=7.2 Hz, 3H); ¹⁹F NMR (471 MHz, CDCl₃) δ -162.69 (s, 1F).

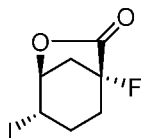
10 Intermediate 1B (±)-1-fluorocyclohex-3-ene carboxylic acid



A mixture of Intermediate 1A (3.80 g, 22.1 mmol) and aq. LiOH (55.2 mL of a 2.0 M solution, 110 mmol) in THF (50 mL) was stirred at rt for 18 h. The reaction was acidified to pH = 2 with conc. HCl (9.19 mL, 110 mmol), and then extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with water and concentrated *in vacuo* to give Intermediate 1B (3.0 g, 20.8 mmol, 94 % yield) as a light yellowish oil. ¹H NMR (500 MHz, CDCl₃) δ 5.81 (ddd, *J*=9.8, 4.6, 2.1 Hz, 1H), 5.66 - 5.58 (m, 1H), 2.76 - 2.59 (m, 1H), 2.49 - 2.37 (m, 1H), 2.35 - 2.23 (m, 1H), 2.22 - 1.92 (m, 3H); ¹⁹F NMR (471 MHz, CDCl₃) δ -163.02 (s, 1F).

20

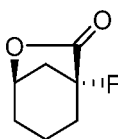
Intermediate 1C (±)-1-fluoro-4-iodo-6-oxabicyclo[3.2.1]octan-7-one



To a mixture of Intermediate 1B (3.0 g, 20.8 mmol) in water (20 mL) was added NaHCO₃ (5.25 g, 62.4 mmol) portionwise and the mixture was stirred until it became homogeneous. An aq. I₂ solution (prepared by dissolving I₂ (5.81 g, 22.0 mmol) and KI (20.7 g, 125 mmol) in 20 mL water) was added and the reaction was stirred overnight at rt in the dark. Water (100 mL) was then added and the mixture was extracted with DCM (3 x 25 mL), washed with 10% aq. Na₂S₂O₃ (20 mL x 2) and water, dried (MgSO₄) and

concentrated *in vacuo*. The residual crude oil was chromatographed (80 g SiO₂) with EtOAc/Hexane (continuous gradient from 0% to 50% EtOAc over 20 min) to give Intermediate 1C (3.53 g, 13.1 mmol, 62.8 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 4.89 (dt, *J*=6.5, 3.5 Hz, 1H), 4.44 (q, *J*=4.6 Hz, 1H), 3.08 (dd, *J*=11.6, 1.9 Hz, 1H), 2.75 (td, *J*=11.3, 6.5, 3.3, 1.1 Hz, 1H), 2.50 - 2.38 (m, 1H), 2.34 - 2.17 (m, 2H), 2.11 - 1.99 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 172.2, 172.0, 93.6, 91.9, 78.4, 78.3, 39.2, 39.0, 29.7, 29.6, 28.4, 28.2, 20.2; ¹⁹F NMR (471 MHz, CDCl₃) δ -167.97 (s, 1F)

Intermediate 1D (±)-1-fluoro-6-oxabicyclo[3.2.1]octan-7-one



10

To a solution of intermediate 1C (350 mg, 1.30 mmol) and AIBN (21 mg, 0.130 mmol) in benzene (5 mL) was added tris(trimethylsilyl)silane (0.60 mL, 1.94 mmol) portionwise over 10 min at 60 °C. The reaction was stirred at 70 °C for 2 h, cooled to rt and then concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with sat. aq. NH₄Cl, dried (MgSO₄) and concentrated *in vacuo*. The crude oil was chromatographed (12 g SiO₂) with EtOAc/Hexane (continuous gradient from 0% to 30% EtOAc over 10 min) to give Intermediate 1D (124 mg, 0.860 mmol, 66.4 % yield) as a white solid. ¹⁹F NMR (471 MHz, CDCl₃) δ -167.01 (s, 1F); ¹H NMR (500 MHz, CDCl₃) δ 4.98 - 4.81 (m, 1H), 2.75 (dt, *J*=15.9, 6.8, 3.3, 1.7 Hz, 1H), 2.24 - 1.89 (m, 5H), 1.82 - 1.65 (m, 1H), 1.60 - 1.46 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.2, 173.0, 93.9, 92.3, 75.6, 75.5, 42.0, 41.9, 31.3, 31.1, 26.7, 17.7, 17.6

20

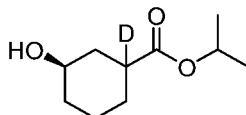
Intermediate 1

Acetyl chloride (0.061 mL, 0.860 mmol) was added portionwise to isopropanol (3 mL) at 0 °C and then stirred at rt for 30 min. Intermediate 1D (124 mg, 0.860 mmol) was added and the reaction was stirred overnight at rt, then was concentrated *in vacuo*. The residual crude oil was chromatographed (4 g SiO₂) with EtOAc/Hexane (continuous gradient from 0% to 50% EtOAc over 10 min) to give Intermediate 1 (140 mg, 0.685 mmol, 80 % yield) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 5.08 (spt, *J*=6.3 Hz, 1H), 3.91 (tt, *J*=10.9, 4.4 Hz, 1H), 2.68 (br. s., 1H), 2.28 (dddt, *J*=13.5, 9.0, 4.6, 2.1 Hz, 1H),

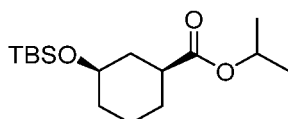
30

2.06 - 1.98 (m, 1H), 1.96 - 1.87 (m, 1H), 1.82 - 1.62 (m, 4H), 1.37 - 1.22 (m, 7H); ^{19}F NMR (471 MHz, CDCl_3) δ -162.93 (s, 1F); ^{13}C NMR (126 MHz, CDCl_3) δ 170.9, 170.7, 95.7, 94.2, 69.3, 66.1, 40.7, 40.5, 33.9, 31.6, 31.4, 21.5, 19.1

5 Intermediate 2 isopropyl (3R)-3-hydroxycyclohexane-1-carboxylate-1-d



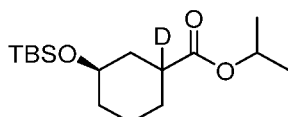
Intermediate 2A isopropyl (1S,3R)-3-((tert-butyltrimethylsilyl)oxy)cyclohexane-1-carboxylate



10

To a solution of (1S,3R)-isopropyl 3-hydroxycyclohexanecarboxylate (0.5 g, 2.68 mmol) and imidazole (0.238 g, 3.49 mmol) in DCM (4 mL) was added tert-butylchlorodimethylsilane (0.486 g, 3.22 mmol) in DCM (1 mL) dropwise over 5 min, stirred at rt overnight. The reaction was diluted with Et_2O (20 mL). The mixture was washed with brine (10 mL); the white aqueous phase was separated and the organic phase was washed with water (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was chromatographed (80 g SiO_2) using a gradient of EtOAc /Hexane (0% to 20% over 15 min) to give (1S,3R)-isopropyl 3-((tert-butyltrimethylsilyl)oxy)cyclohexanecarboxylate (0.60 g, 1.897 mmol, 70.7 % yield) as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 5.08 - 4.95 (m, 1H), 3.65 - 3.51 (m, 1H), 2.40 - 2.21 (m, 1H), 2.09 (d, $J=12.7$ Hz, 1H), 1.94 - 1.76 (m, 3H), 1.50 - 1.35 (m, 1H), 1.34 - 1.17 (m, 9H), 0.91 (s, 9H), 0.13 - 0.05 (m, 6H)

Intermediate 2B isopropyl (1S,3R)-3-((tert-butyltrimethylsilyl)oxy)cyclohexane-1-carboxylate



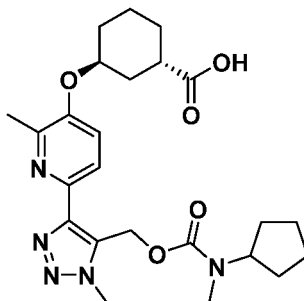
A solution of LDA (1.664 mL, 3.33 mmol) was added under Ar to a solution of intermediate 2A (0.5 g, 1.66 mmol) in THF (6.66 mL) at -78° and the resultant mixture was stirred for 60 min. Then D₂O (0.90 mL, 49.9 mmol) was added and the reaction was allowed to warm to rt. Saturated aq. NH₄Cl (3 mL) was added and the solution was allowed to warm to rt. The reaction mixture was extracted with EtOAc (10 mL), and the combined organic extracts were washed with aq. HCl (10 mL of a 2 M solution), saturated aq. NaHCO₃ and then brine. The organic layer was dried over MgSO₄, filtered, then concentrated *in vacuo* to give an oil as the crude product (used in the next step without further purification) (1S,3R)-isopropyl 3-((tert-butyl-
 5 butyldimethylsilyl)oxy)cyclohexanecarboxylate (0.50 g, 1.66 mmol). LCMS, [M+H]⁺ = 302.1.
 10

Intermediate 2

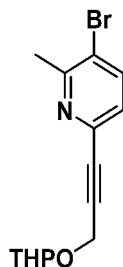
To a solution of intermediate 2B (0.53 g, 1.758 mmol) in THF (3 mL) was added Bu₄NF (3.52 mL of a 1 M solution, 3.52 mmol) at rt and stirred overnight. The reaction
 15 was then quenched with 1.5 M aq. potassium phosphate (10 mL) and extracted with EtOAc (10 mL). The organic extract was concentrated *in vacuo* and chromatographed (24 g SiO₂, continuous gradient from 0 to 100% EtOAc/Hexanes over 30 min, then at 100% EtOAc for 10 min) to give intermediate 2 (0.17 g, 0.908 mmol, 51.6 % yield). ¹H
 20 NMR (500 MHz, CDCl₃) δ 5.02 (dt, *J*=12.6, 6.2 Hz, 1H), 4.11 (t, *J*=4.3 Hz, 1H), 1.84 (d, *J*=4.1 Hz, 3H), 1.77 - 1.68 (m, 1H), 1.65 - 1.49 (m, 5H), 1.24 (d, *J*=6.3 Hz, 6H).

Example 1

(1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-
 25 triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



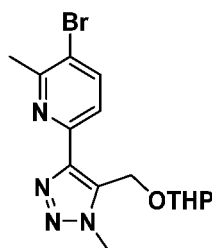
1A 3-bromo-2-methyl-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine



To a solution of 2,5-dibromo-6-methyl-pyridine (5 g, 21.11 mmol) and 2-(prop-2-yn-1-yloxy) tetrahydro-2H-pyran (4.44 g, 31.7 mmol) in MeCN (42.2 mL) was added
 5 Et₃N (8.83 mL, 63.3 mmol). The solution was degassed under N₂, then trans-dichlorobis(triphenylphosphine) palladium (II) chloride (0.74 g, 1.06 mmol) and CuI (0.20 g, 1.06 mmol) were added. The reaction was stirred at rt for 14 h, after which the reaction mixture was filtered through a Celite® plug and the plug was washed with EtOAc (2 X 10 mL). The filtrate was concentrated *in vacuo* and the residue was chromatographed (SiO₂;
 10 continuous gradient from 0% to 100% EtOAc in Hexanes for 20 min) to give the title compound as a white solid (6.0 g, 20.3 mmol, 96 % yield). ¹H NMR (400 MHz, CDCl₃) δ 8.65 (d, *J*=2.0 Hz, 1H), 7.80 (dd, *J*=8.3, 2.3 Hz, 1H), 7.35 (dd, *J*=8.4, 0.4 Hz, 1H), 4.91 (t, *J*=3.3 Hz, 1H), 4.61 - 4.45 (m, 2H), 3.98 - 3.81 (m, 1H), 3.66 - 3.44 (m, 1H), 1.92 - 1.73 (m, 2H), 1.72 - 1.52 (m, 2H). LCMS, [M+H]⁺ = 298.0.

15

1B 3-bromo-2-methyl-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridine



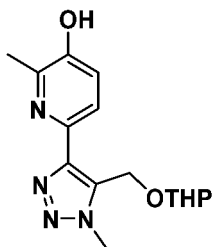
A solution of 1A (6.0 g, 20.3 mmol) in toluene (20 mL) and TMSCH₂N₃ (7.85 g, 60.8 mmol) was heated at 90 °C under Ar for 15 h, then was cooled to rt. Volatiles were removed *in vacuo* and the residue was dissolved in THF (20 mL). To the mixture was added TBAF (20.3 mL of a 1 M solution in THF, 20.3 mmol) at 0 °C. After stirring for 10 min, the reaction was complete as determined by analytical HPLC. Volatiles were

removed *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 (2.1 g, 29 % yield) as a white solid. ¹H NMR (400MHz, CHLOROFORM-d) δ 7.85 (d, *J*=8.4 Hz, 1H), 7.13 (d, *J*=8.4 Hz, 1H), 6.03 (br. s., 1H), 5.39 - 5.23 (m, 4H), 4.81 - 4.76 (m, 1H),
 5 4.17 (s, 3H), 3.91 (ddd, *J*=11.3, 7.9, 3.3 Hz, 1H), 3.65 - 3.48 (m, 1H), 2.54 (s, 3H), 1.88 - 1.68 (m, 2H), 1.56 (br. s., 2H)

Alternatively, 1B can be synthesized by the following procedure:

To a stirred solution of 1A (4.0 g, 13.5 mmol) in DMF (45 mL) under N₂ was
 10 added NaN₃ (2.63 g, 40.5 mmol). The reaction mixture was stirred at 90 °C for 36 h, then was cooled to rt and filtered through Celite®. To the filtrate was added K₂CO₃ (3.73 g, 27.0 mmol) and the reaction mixture was stirred at rt for 10 min. CH₃I (1.27 mL, 20.3 mmol) was added dropwise and the reaction mixture was stirred at rt for 16 h, then was diluted with water (150 mL) and extracted with EtOAc (2 x 100 mL). The combined
 15 organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residual mixture of products (the 2 N-methyl triazole regioisomers) were separated by flash chromatography (40 g Redisep® SiO₂ column, eluting with 21 % EtOAc in hexanes). The desired regioisomer product, title compound 1B, was isolated as a white solid (1.0 g, 21%). LC-MS, [M+2]⁺ = 355.2. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.64 (d, *J*=2.0 Hz,
 20 1H), 8.10 (d, *J*=8.0 Hz, 1H), 7.83 - 7.92 (m, 1H), 5.27 (s, 2H), 4.68 - 4.77 (m, 1H), 4.17 (s, 3H), 3.80 - 3.90 (m, 1H), 3.49 - 3.57 (m, 1H), 1.67 - 1.80 (m, 2H), 1.56 - 1.62 (m, 2H), 1.49 - 1.55 (m, 2H).

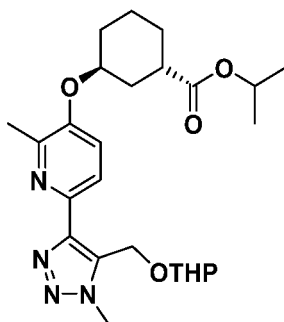
1C 2-methyl-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-ol
 25



To a degassed solution (sparged with Ar 3X) of 1B (213 mg, 0.60 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (230 mg, 0.91 mmol) and KOAc

(178 mg, 1.81 mmol) in THF was added Pd(dppf)Cl₂ (22 mg, 0.03 mmol). The reaction mixture was heated in a sealed tube at 80 °C for 16 h, then was cooled to rt and partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (3 X 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude boronate product was carried on to the next step without further purification. To a solution of the crude product, 2-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (241 mg, 0.603 mmol) in EtOAc (2 mL) was added H₂O₂ (0.19 mL of a 30% aqueous solution, 6.0 mmol). The reaction mixture was stirred at rt for 1h, then was cooled to 0 °C and quenched by slowly adding sat. aq. Na₂S₂O₃. The aqueous layer was extracted with EtOAc (3 X 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was chromatographed (SiO₂, continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give the title compound (150 mg, 86%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, *J*=2.6 Hz, 1H), 8.06 (d, *J*=8.6 Hz, 1H), 7.29 - 7.21 (m, 1H), 5.33 (s, 1H), 5.28 (d, *J*=2.4 Hz, 2H), 4.76 (s, 1H), 4.18 (s, 3H), 3.90 (s, 1H), 3.63 - 3.48 (m, 1H), 1.72 (s, 2H), 1.65 - 1.51 (m, 2H). LCMS, [M+H]⁺ = 291.2.

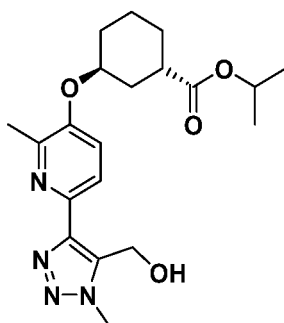
1D. isopropyl (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



To a solution of 1C (1.18 g, 4.06 mmol) and (1S, 3R)-isopropyl 3-hydroxy cyclohexanecarboxylate (synthesized according to the procedure described in US2007/0197788A1, 1.51 g, 8.13 mmol) in toluene (81 mL) was added Bu₃P (3.17 mL, 12.2 mmol). To this stirred mixture was added (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (3.08 g, 12.2 mmol) portionwise, and the reaction mixture was heated at 50

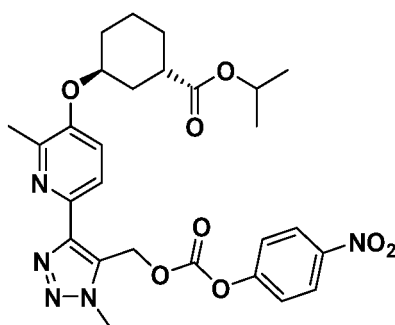
°C for 120 min, then was cooled to rt. At this point an LC-MS of the reaction mixture showed the presence of the desired product. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO₂, continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give the title compound (1.20 g, 2.62 mmol, 64.4 % yield) as a white foam. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, *J*=8.6 Hz, 1H), 7.22 (d, *J*=8.6 Hz, 1H), 5.45 - 5.24 (m, 2H), 5.04 (dt, *J*=12.5, 6.3 Hz, 1H), 4.83 - 4.64 (m, 2H), 4.16 (s, 3H), 3.91 (ddd, *J*=11.2, 7.9, 3.1 Hz, 1H), 3.64 - 3.48 (m, 1H), 2.93 - 2.71 (m, 1H), 2.52 (s, 3H), 2.23 - 1.45 (m, 14H), 1.26 (dd, *J*=6.4, 2.0 Hz, 6H).

- 10 1E. isopropyl (1S,3S)-3-(((6-(5-(hydroxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylate



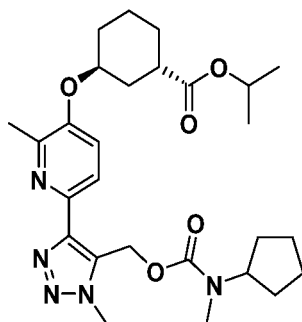
- 15 To a solution of 1D (1.7 g, 3.71 mmol) in MeOH (37 mL) added pyridinium p-toluenesulfonate (0.932 g, 3.71 mmol). The reaction mixture was heated to 60°C for 2h, then was cooled to rt, diluted with water and sat. aq. NaHCO₃, then extracted with EtOAc (3 X 10 mL). The combined organic extracts were concentrated *in vacuo* and chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give the title compound as a white foam (1.36 g, 3.63 mmol, 98 % yield). ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J*=8.6 Hz, 1H), 7.46 (d, *J*=5.1 Hz, 1H), 7.27 - 7.15 (m, 1H), 4.96 (dt, *J*=12.5, 6.3 Hz, 1H), 4.74 (s, 2H), 4.66 - 4.59 (m, 1H), 4.00 (s, 3H), 2.80 - 2.64 (m, 1H), 2.46 (s, 3H), 2.07 - 1.50 (m, 8H), 1.18 (dd, *J*=6.4, 2.2 Hz, 6H).

- 25 1F. isopropyl (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((4-nitrophenoxy)carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



To a solution of 1E (1.36 g, 3.63 mmol) and 4-nitrophenyl chloroformate (2.20 g, 10.9 mmol) in DCM (36.3 mL) was added pyridine (1.47 mL, 18.2 mmol). The reaction mixture was stirred at rt for 2 h. LCMS showed the desired product at this point. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO₂, continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to afford the title compound as a white solid (1.66 g, 3.08 mmol, 85% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.30 (d, *J*=9.2 Hz, 1H), 8.03 (d, *J*=8.4 Hz, 1H), 7.41 (d, *J*=9.2 Hz, 2H), 7.25 (d, *J*=8.6 Hz, 1H), 6.07 (s, 2H), 5.05 (quin, *J*=6.2 Hz, 1H), 4.72 (br. s., 1H), 4.22 (s, 3H), 2.91 - 2.73 (m, 1H), 2.52 (s, 3H), 2.21 - 1.61 (m, 9H), 1.27 (dd, *J*=6.3, 1.9 Hz, 6H).

1G. isopropyl (1S,3S)-3-(((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylate



15

To a solution of 1F (5 g, 9 μmol) and DIPEA (1.5 μL, 9 μmol) in THF (0.5 mL) was added N-methylcyclopentanamine (1 mg, 9 μmol). The reaction mixture was stirred at rt overnight, after which LC-MS showed the desired product. Volatiles were removed *in vacuo* and the residue was dissolved in EtOAc and washed with aq. 1N NaOH (5 x 10 mL) until the yellow color had disappeared. The organic layer was concentrated

20

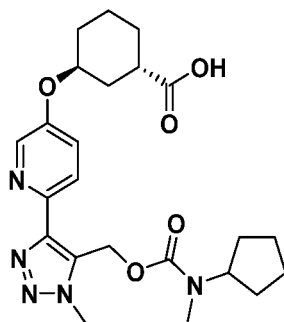
in vacuo. The residue was used for the next step without purification. LCMS, $[M+H]^+ = 514.4$.

Example 1

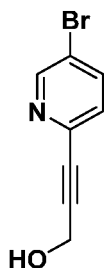
- 5 To a stirred solution of 1G (4.6 mg, 9 μ mol) in THF (0.5 mL), MeOH (0.1 mL) and water (0.1 mL) at rt was added aq LiOH.H₂O (0.023 mL of a 2.0 M solution, 0.045 mmol). The reaction mixture was stirred at 50 °C for 2h, after which LC-MS showed that all starting material had been consumed. The mixture was acidified to pH = ~1 by dropwise addition of 1M aq. HCl. The mixture was extracted with EtOAc (3 x 15 mL);
- 10 the combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative HPLC (PHENOMENEX®, Axia 5 μ C18 30x100 mm column; detection at 220 nm; flow rate=40 mL/min; continuous gradient from 0% B to 100%B over 10 min+2 min hold time at 100% B, where A=90:10:0.1 H₂O:MeOH:TFA and B=90:10:0.1 MeOH:H₂O:TFA) (to give the title compound as an oil (3.2 mg, 75%). LCMS, $[M+H]^+ =$
- 15 472.3. ¹H NMR (500 MHz, DMSO-d₆) δ 7.84 (d, *J*=8.2 Hz, 1H), 7.49 (d, *J*=8.5 Hz, 1H), 5.64 (br. s., 2H), 4.79 (br. s., 1H), 4.10 (s, 3H), 2.66 (br. s., 4H), 2.42 (s, 3H), 2.10 - 1.31 (m, 17H). hLPA1 IC₅₀ = 24 nM. Acute *in vivo* histamine assay in CD-1 mice : -97% histamine at a 3 mg/kg dose of Example 1.

20 Example 2

(1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



- 25 2A. 3-(5-bromopyridin-2-yl)prop-2-yn-1-ol

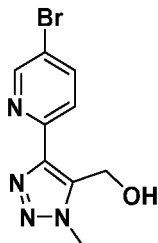


To a solution of 3,6-dibromopyridine (25.0 g, 100 mmol) and prop-2-yn-1-ol (8.70 mL, 149 mmol) in MeCN (141 mL) was added Et₃N (33.2 mL, 240 mmol). The solution was degassed under Ar (sparged with Ar 3X), after which trans-

5 dichlorobis(triphenylphosphine) palladium (II) chloride (2.96 g, 4.22 mmol) and CuI (0.804 g, 4.22 mmol) were added. The reaction was stirred at rt under Ar for 14 h; the mixture was filtered through a Celite® plug, which was washed with EtOAc (3 X 50 mL). The combined filtrates were concentrated *in vacuo*. The residue was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give the title

10 compound as a white solid (16.6 g, 74 % yield). ¹H NMR (400 MHz, CD₃OD) δ 8.60 (d, *J*=2.2 Hz, 1H), 7.99 (dd, *J*=8.4, 2.2 Hz, 1H), 7.44 (d, *J*=8.4 Hz, 1H), 4.41 (s, 2H)

2B (4-(5-bromopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methanol

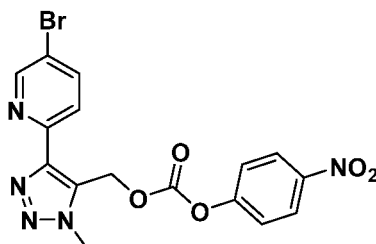


15 To a degassed (sparged with Ar 3X) solution of 2A (1.9 g, 8.40 mmol) in dioxane (42.0 mL) was added chloro(pentamethylcyclopentadienyl)bis (triphenyl-phosphine) ruthenium (II) (0.402 g, 0.504 mmol). The mixture was degassed 3 times under Ar again and TMSCH₂N₃ (1.87 mL, 12.6 mmol) was added. The reaction was stirred at 50 °C for 15 h under Ar, then cooled to rt and concentrated *in vacuo*. The oily residue was

20 dissolved in THF (90 mL) and cooled to 0 °C. TBAF (5.40 mL of a 1.0 M solution in THF; 5.40 mmol) was added and the reaction was stirred at 0 °C for 10 min, after which solid NaHCO₃ (4 g) was added. The reaction mixture was stirred for 30 min at rt and then filtered. The filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give the title

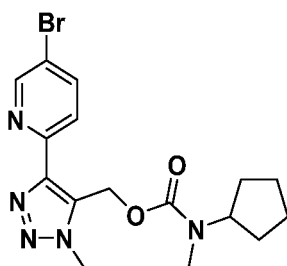
compound (1.30 g, 4.59 mmol, 102 % yield) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.49 (dd, $J=2.3, 0.7$ Hz, 1H), 8.08 (dd, $J=8.5, 0.6$ Hz, 1H), 7.83 (dd, $J=8.5, 2.2$ Hz, 1H), 6.16 (t, $J=6.9$ Hz, 1H), 4.68 (d, $J=6.9$ Hz, 2H), 3.95 (s, 3H).

- 5 2C (4-(5-bromopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl (4-nitrophenyl) carbonate



- To a solution of 2B (1.22 g, 4.31 mmol) in CH_2Cl_2 (50 mL) was added pyridine (1.74 mL, 21.55 mmol) and 4-nitrophenyl chloroformate (1.74 g, 8.62 mmol). The reaction was stirred at rt for 1h, then was concentrated *in vacuo*. The residual solid was trituated with CH_2Cl_2 and filtered to give the pure title compound. The filtrate was concentrated *in vacuo* and the residue was chromatographed (SiO_2 ; continuous gradient from 0% to 100% EtOAc in DCM, 20 min); this purified material was combined with the previously trituated compound to give the title compound as a white solid (1.66 g, 86%).
- 15 LCMS, $[\text{M}+\text{H}]^+ = 434.1$.

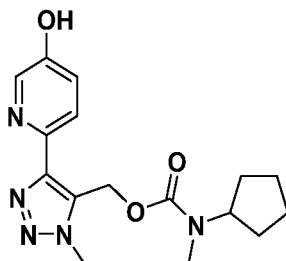
2D. (4-(5-bromopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl cyclopentyl(methyl)carbamate



- To a solution of 2C (140 mg, 0.31 mmol) in THF (6.2 mL) was added $i\text{Pr}_2\text{NEt}$ (109 μL , 0.62 mmol) and 1-cyclobutyl-N-methylmethanamine (31 mg, 0.31 mmol). The reaction was stirred at rt for 2h, then was concentrated *in vacuo*. The residue was chromatographed (SiO_2 ; continuous gradient from 0% to 100% EtOAc in Hexanes, 20

min) to give the title compound as a white solid (100 mg, 78%). ¹H NMR (400 MHz, CDCl₃) δ 8.66 (dd, *J*=2.4, 0.7 Hz, 1H), 8.11 (dd, *J*=8.6, 0.7 Hz, 1H), 7.89 (dd, *J*=8.6, 2.4 Hz, 1H), 5.74 (s, 2H), 4.15 (s, 3H), 2.88 - 2.59 (m, 3H), 1.87 - 1.38 (m, 9H)

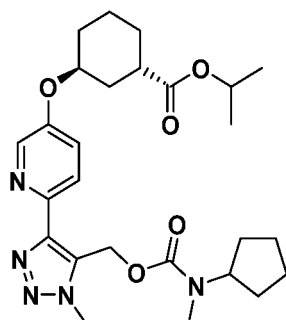
- 5 2E. (4-(5-Hydroxypyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate



- To a degassed (sparged with Ar 3X) solution of 2D (151 mg, 3.70 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.41 g, 5.55 mmol), and
 10 potassium acetate (1.45 g, 14.8 mmol) in THF (25 mL) was added Pd(dppf)Cl₂ (0.271 g, 0.370 mmol) and the reaction was heated at 60 °C overnight under Ar, then cooled to rt. Water (10 mL) was added and the mixture was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (MgSO₄) and concentrated *in vacuo*. The residual crude boronate product was dissolved
 15 in EtOAc (15 mL) and H₂O₂ (1.62 mL of a 30% aq. solution, 18.5 mmol) was carefully added portionwise at 0°C. The reaction was allowed to warm to rt and stirred at rt for 1h, then was cooled 0°C and quenched with sat. aq. Na₂S₂O₃ (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried (MgSO₄) and concentrated *in vacuo*. The residue was
 20 chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give the title compound as a white solid (962 mg, 75%). ¹H NMR (400 MHz, CD₃OD) δ 8.22 (dd, *J*=3.0, 0.6 Hz, 1H), 7.87 (dd, *J*=8.6, 0.7 Hz, 1H), 7.30 (dd, *J*=8.7, 3.0 Hz, 1H), 5.68 (s, 2H), 4.19 (s, 3H), 2.76 (br. s., 3H), 1.92 - 1.43 (m, 8H). LCMS, [M+H]⁺ = 332.3.

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1G. isopropyl (1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



To a solution of 2E (962mg, 2.79 mmol), (1S,3R)-isopropyl 3-hydroxy-cyclohexanecarboxylate (934 mg, 5.01 mmol), and Bu₃P (1.74 mL, 6.96 mmol) in toluene
 5 (55 mL) was added (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (1.76 g, 6.96 mmol). The reaction was heated at 50 °C for 7h, then was cooled to rt. The mixture was diluted with CH₂Cl₂ (20mL) and filtered through Celite®, which was washed with additional CH₂Cl₂ (3 x 20mL). The combined filtrates were concentrated *in vacuo*, and the residue was chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in
 10 Hexanes, 20 min) to give the title compound as a white solid (786 mg, 55%). ¹H NMR (400 MHz, CDCl₃) δ 8.33 (d, *J*=2.6 Hz, 1H), 8.12 (d, *J*=8.6 Hz, 1H), 7.34 (dd, *J*=8.8, 2.9 Hz, 1H), 5.78 (s, 2H), 5.05 (dt, *J*=12.5, 6.3 Hz, 1H), 4.77 - 4.66 (m, 1H), 4.16 (s, 3H), 2.95 - 2.64 (m, 4H), 2.12 - 2.08 (m, 1H), 2.03 - 1.87 (m, 4H), 1.82 - 1.41 (m, 12H), 1.29 - 1.19 (m, 6H). LCMS, [M+H]⁺ = 500.4.

15

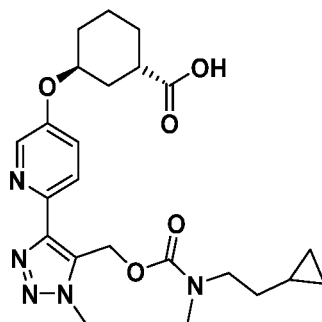
Example 2

To a solution of 2F (786 mg, 1.53 mmol) in THF (3 mL) and MeOH (3 mL) added aq. LiOH (3.06 mL of a 2N solution, 6.12 mmol). The reaction mixture was stirred at rt overnight, after which the pH was adjusted to ~5 and water (10 mL) was added. The
 20 mixture was extracted with EtOAc (3 x 30 mL), washed with water (30 mL) and brine (30 mL), dried (MgSO₄) and concentrated *in vacuo*. The resulting solid was dissolved in 3 mL of EtOAc and allowed to stand overnight to give the title compound as a white crystalline solid (600 mg, 83%). LCMS, [M+H]⁺ = 458.2. ¹H NMR (500 MHz, CD₃CN) δ 8.34 (d, *J*=2.5 Hz, 1H), 8.08 - 8.00 (m, 1H), 7.45 (dd, *J*=8.8, 2.8 Hz, 1H), 5.66 (s, 2H),
 25 4.88 - 4.73 (m, 1H), 4.11 (s, 3H), 2.87 - 2.77 (m, 1H), 2.72 (br. s., 3H), 2.10 - 2.01 (m,

1H), 1.92 - 1.80 (m, 3H), 1.79 - 1.57 (m, 9H), 1.56 - 1.43 (m, 4H). HPLC-1: RT = 7.99 min, purity = 100%; HPLC-2: RT = 7.81 min, purity = 100%. hLPA1 IC₅₀ = 19 nM.

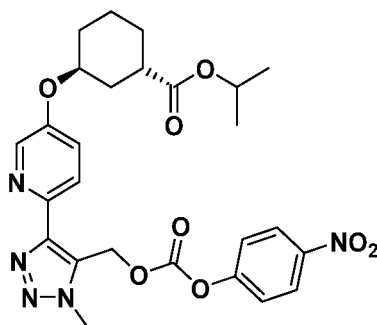
Example 3

- 5 (1S,3S)-3-((6-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



- 3A. Isopropyl (1S,3S)-3-((6-(1-methyl-5-(((4-nitrophenoxy)carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate

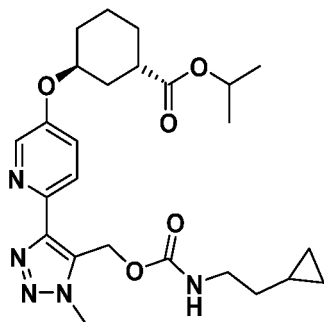
10



- The title compound was prepared by the same synthetic sequence as for Example 1F, except that 2,5-dibromo-pyridine was used as starting material instead of 2,5-dibromo-6-methyl-pyridine. ¹H NMR (400 MHz, CDCl₃) δ 8.43 - 8.25 (m, 3H), 8.23 - 8.10 (m, 1H), 7.47 - 7.31 (m, 3H), 6.11 - 5.77 (m, 2H), 5.20 - 4.95 (m, 1H), 4.79 - 4.63 (m, 1H), 4.31 - 4.19 (m, 3H), 2.92 - 2.71 (m, 1H), 2.12 - 1.54 (m, 8H), 1.35 - 1.20 (m, 6H). LCMS, [M+H]⁺ = 540.2.

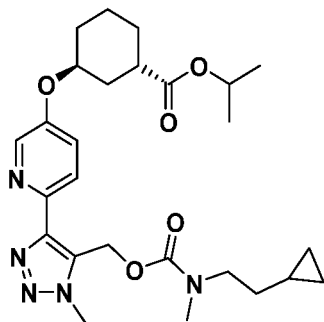
20

3B. isopropyl (1S,3S)-3-((6-(5-(((2-cyclopropylethyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



5 To a solution of Example 3A (10 mg, 9.3 μ mol) and $i\text{Pr}_2\text{NEt}$ (6.5 μ L, 0.037 mmol) in THF (0.5 mL) was added 2-cyclopropyl ethanamine (0.8 mg, 9.3 μ mol). The reaction mixture was stirred at rt overnight, then was concentrated *in vacuo*. The residue was chromatographed (SiO_2 ; continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give the title compound as a white solid (8 mg, 80%). LCMS, $[\text{M}+\text{H}]^+ =$
 10 486.4.

3B. isopropyl (1S,3S)-3-((6-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



15 To a solution of 3A (50 mg, 0.103 mmol) and MeI (0.129 mL, 0.257 mmol) in DMF (0.5 mL) was added NaH (10 mg of a 40% suspension in oil, 0.25 mmol). The reaction was stirred at rt for 1h, then was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (MgSO_4) and concentrated *in vacuo* to give the crude product,
 20 which was used in the next step without further purification. LCMS, $[\text{M}+\text{H}]^+ = 500.4$.
 Example 3

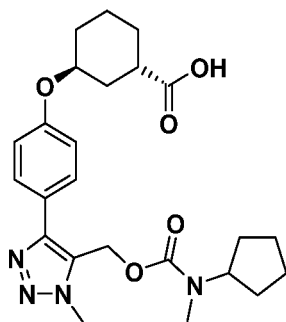
To a stirred solution of 3B (5 mg, 10 μ mol) in THF (1.5 mL), MeOH (0.10 mL) and water (0.15 mL) at rt was added aq. LiOH (0.015 mL of a 2 M solution, 0.030 mmol). The reaction mixture was stirred at 50 °C for 1 h, then was cooled to rt. The mixture was acidified to pH 2.3 by dropwise addition of 1M aq. HCl, then was concentrated *in vacuo*.

5 The residue was purified by preparative HPLC (PHENOMENEX®, Axia 5 μ C18 30x100 mm column; detection at 220 nm; flow rate=40 mL/min; continuous gradient from 0% B to 100%B over 10 min+2 min hold time at 100% B, where A=90:10:0.1 H₂O:MeOH:TFA and B=90:10:0.1 MeOH:H₂O:TFA) (to give the title compound as an oil (4.2 mg, 92%).

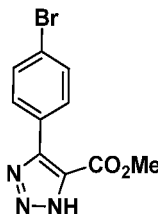
¹H NMR (500 MHz, DMSO- δ_6) δ 8.13 (br. s., 1H), 7.78 (d, *J*=8.2 Hz, 1H), 7.33 (d, *J*=6.4 Hz, 1H), 5.48 - 5.30 (m, 2H), 4.57 (br. s., 1H), 3.89 (br. s., 3H), 3.09 - 2.88 (m, 2H), 2.56 (d, *J*=16.8 Hz, 4H), 2.46 (br. s., 1H), 1.80 - 1.53 (m, 5H), 1.51 - 1.25 (m, 5H), 1.20 - 0.93 (m, 4H). LCMS, [M+H]⁺ = 458.4. HPLC-4: RT = 1.42 min, purity = 100%. hLPA1 IC₅₀ = 19 nM.

15 Example 4

(*rac*)-*trans*-3-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid



4A Methyl 4-(4-bromophenyl)-1H-1,2,3-triazole-5-carboxylate

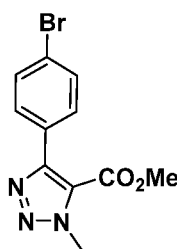


20

To a stirred solution of 4-bromobenzaldehyde (1.0 g, 5.40 mmol), methyl 2-cyanoacetate (0.536 g, 5.40 mmol) and Et₃N.HCl (2.23 g, 16.2 mmol) in DMF (20 mL) under N₂ was added NaN₃ (1.12 g, 17.3 mmol) and the reaction mixture was stirred at 70

°C for 16 h, then was cooled to rt. The reaction mixture was slowly poured into water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 40% EtOAc in n-hexanes) to afford the title compound (0.24 g, 16%) as a yellow solid. LCMS, [M+H]⁺ = 284.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 15.91 (br. s., 1H), 7.75 - 7.85 (m, 4H), 3.82 (m, 3H).

4B Methyl 4-(4-bromophenyl)-1-methyl-1H-1,2,3-triazole-5-carboxylate



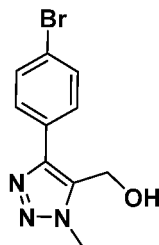
10

To a stirred solution of 4A (250 mg, 0.886 mmol) in MeCN (5 mL) was added K₂CO₃ (122 mg, 0.886 mmol) and the reaction mixture was allowed to stir at rt for 30 min. CH₃I (0.06 mL, 0.886 mmol) was added and the reaction was stirred at rt under N₂ for 16 h. The reaction mixture was diluted with water, extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 30% EtOAc in n-hexanes) to afford the title compound (200 mg, 70%) as an off white solid. ¹H NMR and LCMS showed the presence of a 3:1 ratio of a mixture of triazole regioisomers (with the title compound the as major isomer), which was carried onto the next step without further purification. LC-MS, [M+H]⁺ = 296.0.

15

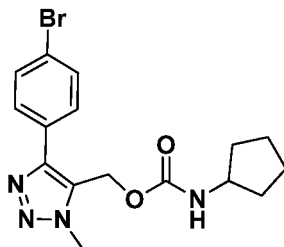
20

4C (4-(4-Bromophenyl)-1-methyl-1H-1,2,3-triazol-5-yl)methanol



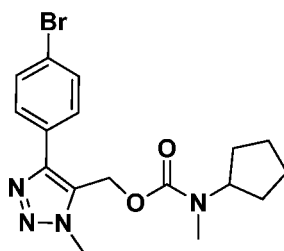
To a solution of mixture of 4B (250 mg, 0.844 mmol) in THF (10 mL) under nitrogen was added dropwise LiAlH (0.93 mL of a 1M solution in THF; 0.93 mmol) at 0 °C and the reaction mixture was allowed to stir at 0 °C for 1h. The reaction was slowly quenched with water (0.5 mL) and aq. NaOH (0.5 mL of a 10% solution). The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (25 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was chromatographed (12 g Redisep® SiO₂ column, eluting with 55 % EtOAc in n-hexanes) to afford the title compound (60 mg, 26%) as an off-white solid. The two regioisomers were separated by preparative HPLC (Column: Symmetry C8 (300 X19)mm 5 µm; M.Phase A: 0.1% HCO₂H in water; M.Phase B: MeCN, flow rate: 17.0 mL/min; time(min)/%B: 0/45, 35/60;). The desired triazole N-methyl regioisomer 4C was isolated as white solid (60 mg 26%) and structurally identified by proton NMR NOE studies on the N-methyl group. LC-MS, [M+H]⁺ = 270.0. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 7.80 - 7.60 (m, 4H), 5.59 (t, *J* = 6.0 Hz, 1H) 4.66 (d, *J* = 3 Hz, 2H), 4.08 (s, 3H).

4D (4-(4-Bromophenyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl cyclopentylcarbamate



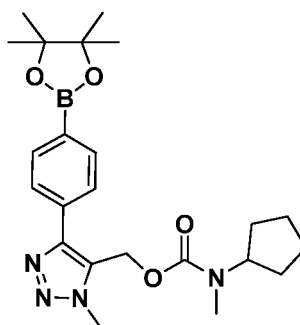
To a stirred solution of cyclopentanecarboxylic acid (63.9 mg, 0.559 mmol) and 4C (150 mg, 0.559 mmol) in toluene (4 mL) were added Et₃N (0.10 mL, 0.84 mmol) and Ph₂PON₃ (0.2 mL, 0.671 mmol), and the resultant solution was stirred at 110 °C for 20h under N₂. The reaction mixture was cooled to rt, volatiles were removed *in vacuo* and the crude product was chromatographed (12 g Redisep® SiO₂ column, eluting with 38% EtOAc in n-hexanes) to afford the title compound (150 mg, 71%) as an off white solid. LC-MS, [M+H]⁺ = 379.0. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.66 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 5.24 (s, 2H), 4.18 (s, 3H), 3.90 - 4.00 (m, 1H), 2.02 - 1.90 (m, 2H), 1.50 - 1.80 (m, 3H), 1.30 - 1.50 (m, 4H).

4E (4-(4-Bromophenyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl
cyclopentyl(methyl)carbamate



To a stirred solution of 4D (200 mg, 0.527 mmol) and DMF (4 mL) was added
5 NaH (19 mg of a 60% suspension in mineral oil, 0.79 mmol) portionwise at 0 °C and the
reaction was stirred at 0 °C for 30 min. Iodomethane (0.049 mL, 0.79 mmol) was added at
0 °C and the reaction was allowed to warm to rt and stirred at rt for 1h. The reaction
mixture was slowly quenched with aq. HCl (5 mL of a 1.5 N solution), diluted with water
(25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were
10 washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude
product was chromatographed (12 g Redisep® SiO₂ column, eluting with 40% EtOAc in
n-hexanes) to afford the title compound (200 mg, 96%) as a pale yellow oily liquid. LC-
MS, [M+H]⁺ = 395.0.

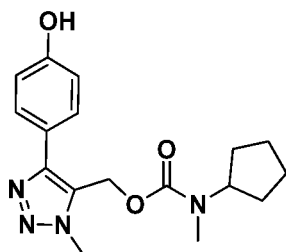
15 4F (1-Methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-1,2,3-triazol-
5-yl)methyl cyclopentyl(methyl)carbamate



To a stirred solution of 4E (700 mg, 1.78 mmol) and bis(pinacolato)diboron (678
mg, 2.67 mmol) in 1,4-dioxane (7 mL) was added KOAc (349 mg, 3.56 mmol) and the
20 reaction mixture was degassed with N₂ for 5 min. 1,1'-Bis(diphenylphosphino)
ferrocenepalladium (II) dichloride-toluene adduct (73 mg, 0.089 mmol) was added and
the reaction mixture was stirred at 90 °C for 16h under N₂. The reaction mixture was
cooled to rt, filtered through a Celite® pad, washed with EtOAc (50 mL) and the

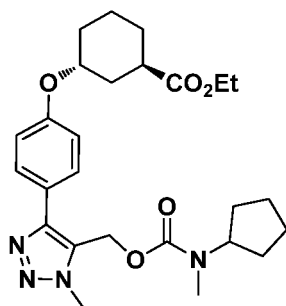
combined organic filtrates were concentrated *in vacuo*. The residue was chromatographed (24 g Redisep[®] SiO₂ column, eluting with 75% EtOAc in n-hexanes) to afford the title compound (700 mg, 89%) as a pale yellow oily liquid. LC-MS, $[M+H]^+ = 441.2$.

- 5 4G (4-(4-Hydroxyphenyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl cyclopentyl(methyl)carbamate



- To a solution of 4F (700 mg, 1.590 mmol) in THF (20 mL) and water (7 mL) mixture was added sodium perborate monohydrate (317 mg, 3.18 mmol) and the reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with sat'd aq. NH₄Cl (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 60 % EtOAc in n-hexanes) to afford the title compound (400 mg, 76%) as a white solid. LC-MS, $[M+H]^+ = 331.2$. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 9.63 (s, 1H), 7.55 (d, *J*=8.7 Hz, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 5.26 (s, 2H), 4.20 - 4.50 (m, 1 H), 4.09 (s, 3H), 2.67 (s, 3H), 1.60 - 1.80 (m, 4H), 1.40 - 1.60 (m, 4H).

- 4H (*rac*)-*trans*-Ethyl 3-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylate

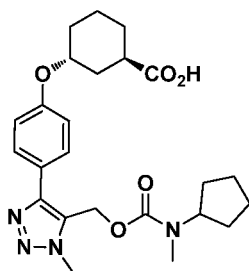


To a stirred solution of 4G (300 mg, 0.908 mmol) and di-*tert*-butyl azodicarboxylate (627 mg, 2.72 mmol) and Ph₃P (714 mg, 2.72 mmol) in THF (10 mL)

under N₂ was added ethyl 3-hydroxycyclohexanecarboxylate (racemic cis isomer; 313 mg, 1.82 mmol) and the reaction mixture was stirred at 60 °C for 16 h under N₂, then was cooled to rt and concentrated *in vacuo*. The residue was chromatographed (24 g Redisep[®] SiO₂ column, eluting with 40% EtOAc in n-hexanes) to afford the title compound (260 mg, 56%) as a colorless oil. LC-MS, [M+H]⁺ = 485.2. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.67 (d, *J*=8.8 Hz, 2H), 7.09 (d, *J*=8.8 Hz, 2H), 5.35 (s, 2H), 4.70 - 4.80 (m, 1H), 4.18 (s, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.70 - 2.90 (m, 1H), 2.75 (s, 3H), 1.80 - 2.10 (m, 4H), 1.40 - 1.80 (m, 13H), 1.10 - 1.30 (t, *J* = 7.2 Hz, 3H).

10 Example 4

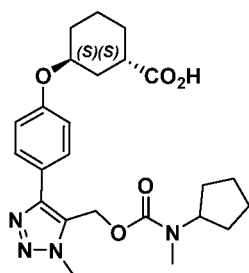
(*rac*)-*trans*-3-(4-(5-(((Cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylic acid



To a stirred solution of 4H (260 mg, 0.429 mmol) in THF (4 mL) and MeOH (4 mL) was added a solution of LiOH·H₂O (31 mg, 1.29 mmol) in water (4 mL) and the reaction mixture was stirred at rt for 16 h. The mixture was diluted with water (20 mL) and washed with Et₂O (20 mL) to remove traces of non-polar impurities. The aqueous layer was neutralized with aq. HCl (2.0 mL of a 1.5N solution) and extracted with 5% MeOH in CHCl₃ (25 mL). The organic layer was washed with brine (25 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Column: Symmetry C8 (300 X19)mm 10 μm; M.Phase A: 0.1% HCOOH in water; M.Phase B: MeCN, flow rate: 17.0 mL/min; time(min)/%B: 0/30, 20/100;) to afford the title compound (120 mg, 45%) as a white solid. LC-MS, [M+H]⁺ = 457.2. ¹H NMR (400 MHz, CD₃OD) δ 7.66 (d, *J* = 8.40 Hz, 2H), 7.09 (d, *J* = 8.80 Hz, 2H), 5.37 (s, 2H), 4.75-4.76 (m, 1H), 4.31-4.50 (m, 1H), 4.20 (s, 3H), 2.77-2.81 (m, 4H), 2.07-2.10 (m, 1H), 1.82-1.97 (m, 3H), 1.49-1.79 (m, 12H). hLPA1 IC₅₀ = 18 nM.

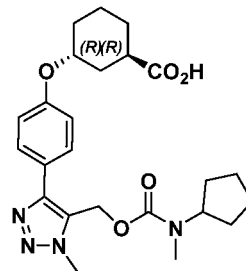
Example 5 and Example 6

Example 5



(1*S*,3*S*)-3-(4-(5-
(((Cyclopentyl(methyl)carbamoyl)oxy)methyl)-
1-methyl-1*H*-1,2,3-triazol-4-
yl)phenoxy)cyclohexanecarboxylic acid

Example 6



(1*R*,3*R*)-3-(4-(5-
(((Cyclopentyl(methyl)carbamoyl)oxy)methyl)-
1-methyl-1*H*-1,2,3-triazol-4-
yl)phenoxy)cyclohexanecarboxylic acid

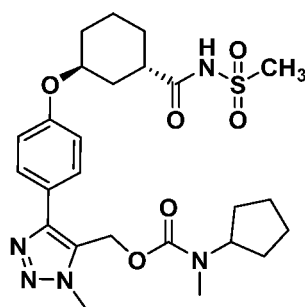
Individual enantiomers of Example 4 was separated by chiral SFC (Column/
dimensions: Chiralpak IC (250 X 21)mm, 5 μ m; % CO₂: 60%; % Co solvent: 40%(0.25%
DEA in MeOH); Total Flow: 60 g/min; Back Pressure: 100 bars; Temperature: 25°C;

- 5 UV: 250 nm;). Example 5 (37 mg, 18%) was isolated as a white solid. LC-MS, [M+H]⁺
= 457.2. OR [α]_D²⁴ = (+)14.0 (c 0.10, MeOH). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.66
(d, *J* = 8.40 Hz, 2H), 7.09 (d, *J* = 8.40 Hz, 2H), 5.37 (s, 2H), 4.75 - 4.76 (m, 1H), 4.31 -
4.50 (m, 1H), 4.20 (s, 3H), 2.77 - 2.81 (m, 4H), 2.07 - 2.10 (m, 1H), 1.82-1.97 (m, 3H),
1.49 - 1.79 (m, 12H). hLPA1 IC₅₀ = 6 nM. Acute mouse in vivo histamine assay: -90%
10 histamine at a 3 mg/kg dose of Example 5. Example 6 (35 mg, 17%) was isolated as a
white solid. LC-MS, [M+H]⁺ = 457.2. OR [α]_D²⁵ = (-)14.0 (c 0.10, MeOH). ¹H NMR
(400 MHz, CD₃OD) δ 7.66 (d, *J* = 8.40 Hz, 2H), 7.09 (d, *J* = 8.40 Hz, 2H), 5.37 (s, 2H),
4.75 - 4.76 (m, 1H), 4.31 - 4.50 (m, 1H), 4.20 (s, 3H), 2.77 - 2.81 (m, 4H), 2.07 - 2.10 (m,
1H), 1.82 - 1.97 (m, 3H), 1.49 - 1.79 (m, 12H). hLPA1 IC₅₀ = 1314 nM.

15

Example 7

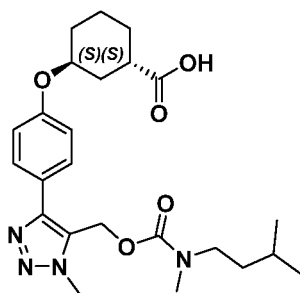
(1-Methyl-4-(4-(((1*S*,3*S*)-3-((methylsulfonyl)carbamoyl)cyclohexyl)oxy)phenyl)-1*H*-
1,2,3-triazol-5-yl)methyl cyclopentyl(methyl)carbamate



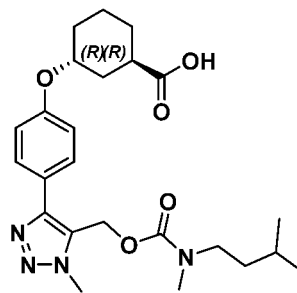
- To a stirred solution of Example 5 (10 mg, 0.022 mmol) and methane sulfonamide (3 mg, 0.033 mmol) in DCM (0.5 mL) and DMF (0.5 mL) mixture was added 4-dimethylaminopyridine (3.21 mg, 0.026 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.30 mg, 0.033 mmol) and the reaction mixture was stirred at rt for 16 h under N₂. The reaction mixture was concentrated *in vacuo* and the crude product was purified by preparative HPLC (Column: Sunfire C18 (150 X19)mm 5 micron; M.Phase A: 0.1% HCO₂H in water; M.Phase B: MeCN, flow rate: 16.0 mL/min; time(min)/%B: 0/30, 30/100;) to afford the title compound (4 mg, 33%) as a white solid.
- LC-MS, [M+H]⁺ = 534.4. ¹H NMR (400 MHz, CD₃OD) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 5.37 (s, 2H), 4.20 (s, 3H), 3.20 (s, 3H), 2.78 - 2.89 (m, 5H), 1.59 - 2.10 (m, 17H). hLPA1 IC₅₀ = 3750 nM.

Example 8 & Example 9

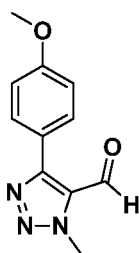
Example 8



Example 9

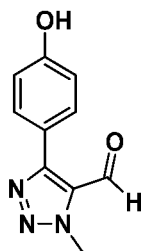


8A 4-(4-Methoxyphenyl)-1-methyl-1-*H*-1,2,3-triazole-5-carboxaldehyde



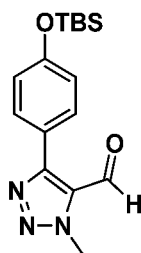
To a stirred solution of 4-(4-methoxyphenyl)-1-methyl-1*H*-1,2,3-triazole (35 g, 185 mmol) in THF (860 mL) under N₂ was added n-BuLi (111 mL of a 2.5 M solution in hexanes, 277 mmol) dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 1h. DMF (22 mL, 277 mmol) was added at -78 °C and the reaction mixture was allowed to slowly warm to rt and stirred for 2h at rt. The reaction mixture was cooled to 0 °C, then was slowly quenched with sat'd aq. NH₄Cl and extracted with DCM (3 x 250 mL). The combined organic extracts were washed with brine (500 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was chromatographed (330 g Redisep[®] SiO₂ column, eluting with 20% EtOAc in n-hexanes) to afford the title compound (18.0 g, 48%) as a yellow solid. LC-MS, [M+H]⁺ = 218.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.04 (s, 1H), 7.84 (d, *J*=9.0 Hz, 2H), 7.10 (d, *J*=9.0 Hz, 2H), 4.31 (s, 3H), 3.84 (s, 3H).

8B 4-(4-Hydroxyphenyl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde



To a stirred solution of 8A (8.4 g, 38.7 mmol) in DCM (160 mL) was added dropwise BBr₃ (11 mL, 116 mmol) at 0 °C and the reaction mixture was stirred at 0 ° for 1h. The reaction mixture was quenched carefully with ice-cold water and neutralized with 10% aq. NaHCO₃ and extracted with DCM (3 x 150 mL). The combined organic extracts were washed with brine (250 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was diluted with DCM and the resulting solid that formed was filtered and dried *in vacuo* to afford the title compound (5.7 g, 73%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 10.04 (s, 1H), 9.88 (s, 1H), 7.71 (d, *J*=13.0 Hz, 2H), 6.92 (d, *J*=13.0 Hz, 2H), 4.28 (s, 3H).

8C 4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde



To a stirred solution of 8B (1.0 g, 4.92 mmol) and imidazole (0.670 g, 9.84 mmol) in DMF (20 mL) was added TBSCl (0.890 g, 5.91 mmol) and the reaction mixture was stirred at rt for 16 h under N₂. Water (100 mL) was added to the mixture, which was
 5 extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine (150 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was chromatographed (24 g Redisep[®] SiO₂ column, eluting with 25 % EtOAc in n-hexanes) to afford the title compound (1.2 g, 77%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ ppm 10.07 (s, 1H), 7.63 (d, *J*=8.7 Hz, 2H), 6.99 (d, *J*=8.7 Hz, 2H), 4.36 (s, 3H),
 10 1.01 (s, 9H), 0.24 (s, 6H).

15

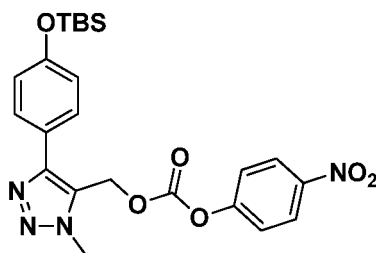
8D (4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methanol



To a 0 °C solution of 8C (1.25 g, 3.94 mmol) in THF (30 mL) was added NaBH₄
 20 (0.223 g, 5.91 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (75 mL) and extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine (150 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was chromatographed (24 g Redisep[®] SiO₂ column, eluting with 60 % EtOAc in n-hexanes) to afford the title compound (0.7 g, 56%)

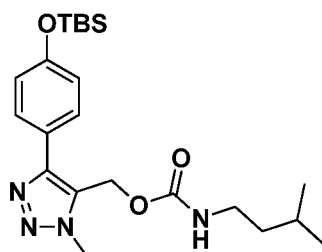
as a white solid. LC-MS, $[M+H]^+ = 320.3$. ^1H NMR (300 MHz, CD_3OD) δ ppm 7.59 (d, $J=8.7$ Hz, 2H), 6.97 (d, $J=8.7$ Hz, 2H), 4.77 (s, 2H), 4.15 (s, 3H), 1.02 (s, 9H), 0.24 (s, 6H).

- 5 8E (4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl (4-nitrophenyl) carbonate



- To a stirred solution of 8D (500 mg, 1.565 mmol) and $i\text{Pr}_2\text{NEt}$ (0.50 mL, 3.13 mmol) in DCM (10 mL) was added 4-nitrophenyl chloroformate (379 mg, 1.88 mmol) at
 10 0 °C and the resultant pale yellow solution was stirred at rt for 16 h under N_2 . The reaction mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was chromatographed (24 g Redisep[®] SiO_2 column, eluting with 40% EtOAc in *n*-hexanes) to afford the title compound (260 mg, 35%) as a white solid. LC-
 15 MS, $[M+H]^+ = 485.2$. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.30 (d, $J=9.0$ Hz, 2H), 7.64 (d, $J=9.0$ Hz, 2H), 7.40 (d, $J=9.0$ Hz, 2H), 6.96 (d, $J=8.5$ Hz, 2H), 5.47 (s, 2H), 4.22 (s, 3H), 1.00 (s, 9H), 0.23 (s, 6H).

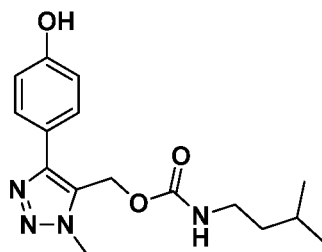
- 8F (4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl
 20 isopentylcarbamate



To a stirred solution of 8E (240 mg, 0.496 mmol) and Et_3N (0.20 mL, 1.49 mmol) in THF (10 mL) was added 3-methylbutan-1-amine (86 mg, 0.991 mmol) and the reaction mixture was stirred at rt for 16 h under N_2 , then was concentrated *in vacuo*. The crude

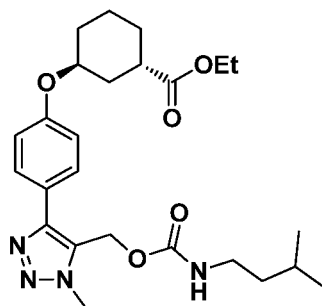
product was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 65% EtOAc in n-hexanes) to afford the title compound (150 mg, 70%) as a pale yellow liquid. LC-MS, [M+H]⁺ = 433.4. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.62 (d, *J*=8.5 Hz, 2H), 6.92 (d, *J*=8.5 Hz, 2H), 5.24 (s, 2H), 4.72 (br. s., 1H), 4.16 (s, 3H), 3.27 - 3.19 (m, 2H), 1.30 - 1.50 (m, 3H), 0.97 - 1.00 (s, 9H), 0.91 - 0.96 (m, 6H), 0.23 (s, 6H).

8G (4-(4-Hydroxyphenyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl isopentylcarbamate



To a stirred solution of 8F (150 mg, 0.347 mmol) in THF (6 mL) was added TBAF (0.52 mL of a 1M solution in THF; 0.52 mmol,) at 0 °C and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 85% EtOAc in n-hexanes) to afford the title compound (90 mg, 82%) as a white solid. LC-MS, [M+H]⁺ = 319.2. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.56 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.4 Hz, 2H), 5.28 (s, 2H), 4.19 (s, 3H), 3.15 (t, *J*=7.3 Hz, 2H), 1.55 - 1.70 (m, 1H), 1.40 (q, *J*=7.0 Hz, 2H), 0.94 (d, *J*= 6.4 Hz, 6H).

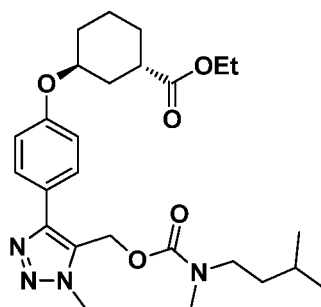
8H (*rac*)-*trans*-(Ethyl 3-(4-(5-(((isopentylcarbamoyl)oxy)methyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylate



To a stirred solution of 8G (100 mg, 0.314 mmol), di-*tert*-butyl azodicarboxylate (217 mg, 0.942 mmol) and Ph₃P (247 mg, 0.942 mmol) in THF (10 mL) under N₂ was added ethyl 3-hydroxycyclohexanecarboxylate (racemic *cis* isomer; 135 mg, 0.785 mmol) and the reaction mixture was stirred at 60 °C for 16 h under N₂, then was cooled to rt.

- 5 The reaction mixture was concentrated *in vacuo* and the crude product was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 22% EtOAc in n-hexanes) to afford the title compound (90 mg, 60%) as a pale yellow liquid. LC-MS, [M+H]⁺ = 473.2. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.66 (d, *J*=9.0 Hz, 2H), 7.09 (d, *J*=9.0 Hz, 2H), 5.29 (s, 2H), 4.75 (br. s., 1H), 4.20 (s, 3H), 4.13 (q, *J*= 6.4 Hz, 2H), 3.15 (t, *J*=7.3 Hz, 2H),
10 2.80 - 2.90 (m, 1H), 1.60 - 2.00 (m, 6H), 1.20 - 1.35 (m, 9H), 0.93 (d, *J*=6.4 Hz, 6H).

8I (*rac*)-*trans*-Ethyl 3-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylate



- 15 To a stirred solution of 8H (90 mg, 0.190 mmol) in DMF (3 mL) under N₂ was added NaH (9 mg of a 60% mineral suspension, 0.38 mmol) portionwise at 0°C and stirred at 0°C for 30 min. Iodomethane (0.020 mL, 0.29 mmol) was then added and the reaction mixture was allowed to warm to rt & stirred at rt for 1h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 25 mL). The combined
20 organic extracts were washed with brine (50 mL), dried (Na₂SO₄), and filtered. The combined filtrates were concentrated *in vacuo*. The crude product was purified by combiflash chromatography (12 g Redisep[®] SiO₂ column, eluting with 75% EtOAc in n-hexanes) to afford the title compound (60 mg, 64%) as a pale yellow liquid. LC-MS, [M+H]⁺ = 487.2.

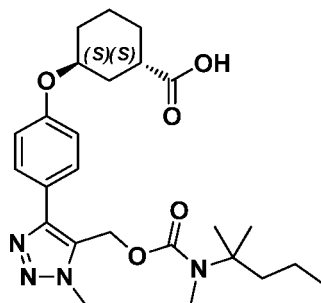
25

Example 8 & Example 9

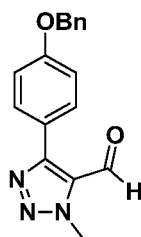
To a stirred solution of 8I (50 mg, 0.103 mmol) in THF (2 mL) and MeOH (2 mL) mixture was added a solution of LiOH.H₂O (7.0 mg, 0.308 mmol) in water (2 mL) and the reaction mixture was stirred at rt for 16 h under N₂. The reaction mixture was diluted with water (20 mL) and washed with Et₂O (20 mL) to remove non-polar impurities. The aqueous layer was neutralized with aq. HCl (2.0 mL of a 1.5 N solution) and extracted with MeOH in CHCl₃ (5% of a 25 mL mixture). The organic layer was washed with brine (25 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Column: Sunfire C18 (250 X30)mm 5 μm; M.Phase A: 10 mM NH₄OAc in water; M.Phase B: MeCN, flow rate: 15.0 mL/min; time(min)/%B: 0/30, 8/40;) followed by separation of individual enantiomers by chiral SFC. Example 8 (17 mg, 28%) was obtained as a gummy solid. LC-MS, [M+H]⁺ = 459.2. OR [α]^{25.1}_D = (+)10.0 (c 0.10, MeOH). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.64 - 7.70 (m, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 5.36 - 5.38 (m, 2H), 4.72 - 4.75 (m, 1H), 4.21 (s, 3H), 3.23 - 3.26 (m, 1H), 2.82 - 2.90 (m, 4H), 2.06 - 2.11 (m, 1H), 1.92 - 1.94 (m, 3H), 1.57 - 1.80 (m, 4H), 1.31 - 1.45 (m, 4H), 0.82 - 0.96 (m, 6H). hLPA1 IC₅₀ = 87 nM. Example 9 (14 mg, 24%) was obtained as a gummy solid. LC-MS, [M+H]⁺ = 459.2. OR [α]^{25.1}_D = (-)2.0 (c 0.10, MeOH). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.64 - 7.70 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.36 - 5.38 (m, 2H), 4.72 - 4.75 (m, 1H), 4.21 (s, 3H), 3.23 - 3.26 (m, 1H), 2.82 - 2.90 (m, 4H), 2.06 - 2.11 (m, 1H), 1.92 - 1.94 (m, 3H), 1.57 - 1.80 (m, 4H), 1.31 - 1.45 (m, 4H), 0.82 - 0.96 (m, 6H). hLPA1 IC₅₀ = 65 nM.

Example 10

(1*S*,3*S*)-3-(4-(1-Methyl-5-(((methyl(2-methylpentan-2-yl)carbamoyl)oxy)methyl)-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylic acid



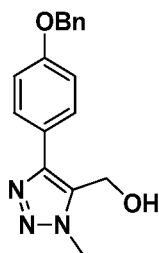
10A 4-(4-(Benzyloxy)phenyl)-1-methyl-1*H*-1,2,3-triazole-5-carbaldehyde



To a stirred mixture of compound 8B (5.5 g, 27.1 mmol) and K_2CO_3 (5.61 g, 40.6 mmol) in MeCN (60 mL) was added benzyl bromide (3.54 mL, 29.8 mmol) at rt and the reaction mixture was stirred at 70 °C for 3 h under N_2 , then was cooled to rt. The reaction mixture was filtered through a Celite® pad, which was washed with DCM (200 mL). The combined filtrates was concentrated *in vacuo* to afford the title compound (7.50 g, 80%) as a pale yellow solid, which was carried onto to the next step without further purification. LC-MS, $[M+H]^+ = 294.2$. 1H NMR (400 MHz, $CDCl_3$) δ ppm 10.06 (s, 1H), 7.71 (d, $J=8.8$ Hz, 2H), 7.33 - 7.49 (m, 5H), 7.12 (d, $J=8.8$ Hz, 2H), 5.15 (s, 2H), 4.37 (s, 3H).

15

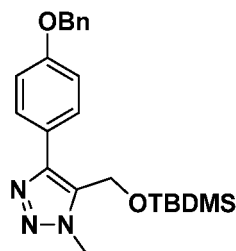
10B (4-(4-(Benzyloxy) phenyl)-1-methyl-1H-1,2,3-triazol-5-yl)methanol



To a stirred solution of 10A (8 g, 27.3 mmol) in THF (60 mL) and MeOH (60 mL) was added portionwise $NaBH_4$ (1.14 g, 30.0 mmol) at 0 °C under N_2 and the reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with sat'd. aq. NH_4Cl (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (400 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (7.0 g, 83%) as a white solid. This crude product was carried on to the

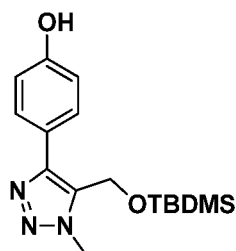
next step without further purification. LC-MS, $[M+H]^+ = 296.2$. ^1H NMR (300 MHz, CDCl_3) δ ppm 7.57 (d, $J=9.0$ Hz, 2H), 7.47 - 7.33 (m, 5H), 7.04 (d, $J=9.0$ Hz, 2H), 5.10 (s, 2H), 4.81 (d, $J=4.2$ Hz, 2H), 4.08 (s, 3H), 2.77 (t, $J=5.4$ Hz, 1H).

- 5 10C 4-(4-(Benzyloxy) phenyl)-5-(((*tert* butyldimethylsilyl) oxy) methyl)-1-methyl-1*H*-1,2,3-triazole



- To a stirred solution of 10B (7 g, 23.70 mmol) and imidazole (4.84 g, 71.1 mmol) in DMF (100 mL) was added TBSCl (4.29 g, 28.4 mmol) and the reaction mixture was stirred at rt for 3h under N_2 . The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (400 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (8.0 g, 77%) as a pale yellow solid. This crude product 10c was used in the next step without further purification. LC-MS, $[M+H]^+ = 410.2$. ^1H NMR (300 MHz, CDCl_3) δ ppm 8.03 (s, 1H), 7.61 (d, $J=9.0$ Hz, 2H), 7.33 - 7.50 (m, 5H), 7.12 (d, $J=9.0$ Hz, 2H), 5.11 (s, 2H), 4.81 (s, 2H), 4.13 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).
- 10 15

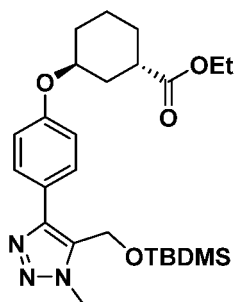
10D 4-(5-(((*tert*-Butyldimethylsilyl) oxy) methyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)phenol



- To a degassed (N_2 was bubbled in for 10 min) solution of 10C (8.0 g, 19.53 mmol) in MeOH (150 mL) was added 10% Pd/C (1 g, 0.940 mmol) at rt. The reaction mixture was degassed with H_2 for 5 min. then was stirred at rt under 1 atm of H_2 for 5h, then the H_2 atmosphere was evacuated and replaced with N_2 . The reaction mixture was filtered through a Celite[®] pad and washed with MeOH (200 mL). The combined filtrates
- 20

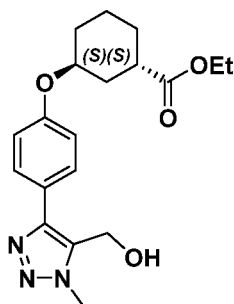
was concentration *in vacuo* to afford the title compound (5.0 g, 76 %) as a white solid. This crude product 10D was used in the next step without further purification. LC-MS, $[M+H]^+ = 320.2$.

- 5 10E (*rac*)-*trans*-Ethyl 3-(4-(5-(((*tert*-butyldimethylsilyl) oxy)methyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylate



- To a stirred solution of 10D (2.75 g, 8.61 mmol), di-*tert*-butyl azodicarboxylate (7.93 g, 34.4 mmol) and Ph_3P (9.03 g, 34.4 mmol) in THF (80 mL) was added (*rac*)-*cis*-ethyl 3-hydroxycyclohexanecarboxylate (5.93 g, 34.4 mmol) and the reaction mixture was stirred at 60 °C for 16h under N_2 , then was cooled to rt. The reaction mixture was concentrated *in vacuo*. The crude product was chromatographed (120 g Redisep[®] SiO_2 column, eluting with 40% EtOAc in n-hexanes) to afford the title compound (2.7 g, 65%) as a colorless liquid. LC-MS, $[M+H]^+ = 474.2$.

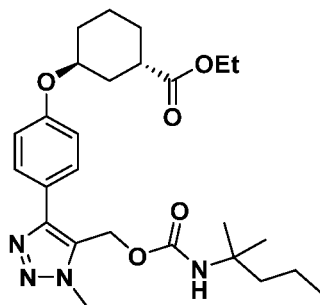
- 15 10F (1*S*,3*S*)-ethyl 3-(4-(5-(hydroxymethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylate



- To a stirred solution 10E (200 mg, 0.211 mmol) in THF (6 mL) was added TBAF (0.317 mL of a 1M solution in THF; 0.317 mmol) at 0 °C and the reaction mixture was stirred at rt under N_2 for 30 min. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with

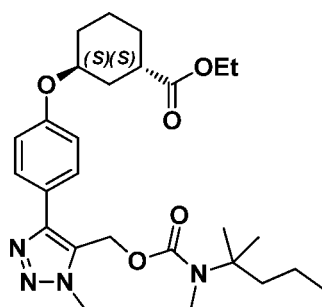
brine (40 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 75% EtOAc in n-hexanes). The racemic product thus obtained was separated by chiral SFC (Luxcellulose-2 (250 X 21.5)mm, 5 μm; % CO₂: 70%; % Co-solvent: 30% (0.25% DEA in MeOH); Total Flow: 70 g/min; Back Pressure: 100 bars; Temperature: 35°C; UV: 230 nm;). The desired S,S enantiomer 10F was isolated (40 mg, 50%) as an off-white solid: LC-MS, [M+H]⁺ = 360.2. Optical rotation [α]_D²⁵ = (+)30 (c 0.10, MeOH). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.63 (d, *J*=8.4 Hz, 2H), 7.09 (d, *J*=8.4 Hz, 2H), 4.79 (s, 2H), 4.72 - 4.76 (m, 1H), 4.18 (s, 3H), 4.16 (q, *J*=7.0 Hz, 2H), 2.80 - 2.88 (m, 1H), 2.03 - 2.11 (m, 1H), 1.88 - 1.98 (m, 3H), 1.57 - 1.82 (m, 4H), 1.25 - 1.30 (m, 3H).

10G (1*S*,3*S*)-Ethyl-3-(4-(1-methyl-5-(((2-methylpentan-2-yl) carbamoyl)oxy)methyl)-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylate



To a solution of 10F (50 mg, 0.14 mmol), 2,2-dimethylpentanoic acid (18 mg, 0.139 mmol) and Et₃N (0.029 mL, 0.21 mmol) in toluene (3 mL) was added Ph₂PON₃ (0.036 mL, 0.167 mmol) and the resultant pale yellow solution was stirred at 110 °C for 16 h under N₂, then was cooled to rt. The reaction mixture was concentrated *in vacuo* and the crude product was chromatographed (12 g Redisep[®] SiO₂ column, eluting with 50% EtOAc in n-hexanes) to afford the title compound (40 mg, 50%) as a white solid. LC-MS, [M+H]⁺ = 487.2. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.65 (d, *J*=9.2 Hz, 2H), 7.08 (d, *J*=9.2 Hz, 2H), 5.24 (s, 2H), 4.75 (br. s., 1H), 4.19 (s, 3H), 4.16 (q, *J*=7.2 Hz, 2H), 3.15 (s, 1H), 2.86 (d, *J*=11.0 Hz, 2H), 2.07 (br. s., 1H), 1.89 - 1.99 (m, 3H), 1.60 - 1.80 (m, 4H), 1.20 - 1.40 (m, 8H), 0.95 - 0.88 (m, 6H).

10H (1*S*,3*S*)-Ethyl 3-(4-(1-methyl-5-(((methyl(2-methylpentan-2-yl)carbamoyl)oxy)methyl)-1*H*-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylate



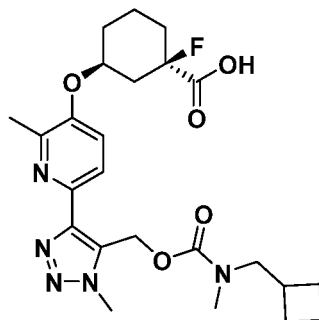
To a stirred solution of 10G (40.0 mg, 0.082 mmol) in DMF (3 mL) under N₂ was added NaH (4 mg of a 60% mineral suspension, 0.16 mmol) portionwise at 0 °C and stirred for 30 min. Iodomethane (7.71 µl, 0.123 mmol) was then added and the reaction mixture was stirred at rt for 1h, then was diluted with water (20 mL). The mixture was extracted with EtOAc (2 x 20 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was chromatographed (12 g Redisep® SiO₂ column, eluting with 75% EtOAc in n-hexanes) to afford the title compound (30 mg, 73%) as a pale yellow liquid. LC-MS, [M+H]⁺ = 501.2.

Example 10

To a stirred solution of 10H (30.0 mg, 0.060 mmol) in THF (1.5 mL) and MeOH (1.5 mL) was added a solution of LiOH·H₂O (4.3 mg, 0.18 mmol) in water (1.5 mL) and the reaction mixture was stirred at rt for 16 h under N₂. The reaction mixture was diluted with water (20 mL) and washed with Et₂O (20 mL) to remove traces of nonpolar impurities. The aqueous layer was neutralized with aq. HCl (2.0 mL of a 1.5 N solution) and extracted with 5% MeOH in CHCl₃ (25 mL). The organic layer was washed with brine (25 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residual crude product was purified by preparative HPLC (Kinetex Biphenyl 100A (2500 X21.1)mm 5 µm; Mobile Phase A: 0.1% HCO₂H in water; Mobile Phase B: MeCN, flow rate: 18.0 mL/min; time(min)/%B: 0/40, 32/75, 35/95;) to afford the title compound (8 mg, 28%) as a white solid. LC-MS, [M+H]⁺ = 473.2. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.63 (d, *J* = 8.80 Hz, 2H), 7.07 (d, *J* = 8.80 Hz, 2H), 5.31 (s, 2H), 4.83 - 4.89 (m, 1H), 4.18 (s, 3H), 2.85 (s, 3H), 2.72 - 2.76 (m, 1H), 2.06 - 2.10 (m, 1H), 1.82 - 1.95 (m, 3H), 1.40 - 1.77 (m, 6H), 1.29 (s, 6H), 1.11 - 1.24 (m, 2H), 0.08 - 0.84 (m, 3H). hLPA1 IC₅₀ = 23 nM.

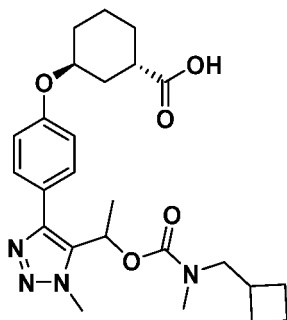
Example 11

(*rac*)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid

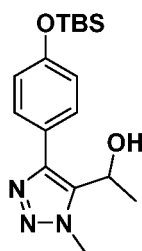


Example 11 was prepared according to the procedure of Example 2 by using
 5 Intermediate 1 instead of (1S,3R)-isopropyl 3-hydroxy-cyclohexanecarboxylate in the
 procedure (Mitsunobu reaction) to synthesize Example 2F. ¹H NMR (400 MHz, CDCl₃) δ
 8.15 (d, *J*=8.8 Hz, 1H), 8.00 - 7.89 (m, 1H), 5.53 - 5.32 (m, 2H), 5.00 (br. s., 1H), 4.21 (d,
J=2.4 Hz, 3H), 3.32 (dd, *J*=10.8, 7.5 Hz, 2H), 2.92 (d, *J*=13.6 Hz, 3H), 2.75 (d, *J*=2.6 Hz,
 3H), 2.55 (dt, *J*=15.5, 7.8 Hz, 1H), 2.47 - 2.27 (m, 1H), 2.24 - 1.77 (m, 10H), 1.76 - 1.58
 10 (m, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ -76.0 (s, F from TFA), -154.4 (s, 1F). LC-MS,
 [M+H]⁺ = 490.4. hLPA1 IC₅₀ = 12 nM.

Example 12 (1S,3S)-3-(4-(5-(1-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)ethyl)-1-
 15 methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric
 mixture)



12A 1-(4-(4-(((tert-butyl)dimethylsilyl)oxy)phenyl)-1-methyl-1H-1,2,3-triazol-5-yl)ethan-
 1-ol



To a -40 °C solution of 8C (279 mg, 0.879 mmol) in THF (18 mL) was added CH₃MgBr (439 μL of a 3 M solution in THF, 1.32 mmol). The reaction mixture was allowed to warm to rt and stirred at rt for 1 h. Water (15 mL) was added and the mixture was extracted with EtOAc (2 X 30 mL). The combined organic extracts were concentrated *in vacuo* and chromatographed (SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes, 20 min) to give 12A (230 mg, 78%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J*=8.8 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 5.33 (dd, *J*=6.8, 3.5 Hz, 1H), 4.23 (s, 3H), 1.96 (d, *J*=3.3 Hz, 1H), 1.64 (d, *J*=6.8 Hz, 3H), 1.00 (s, 9H), 0.22 (s, 6H)

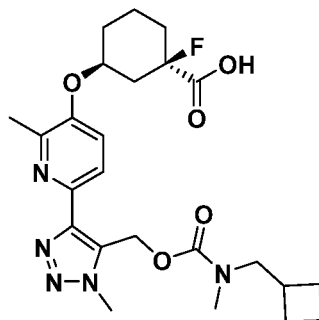
10

Example 12 was prepared according to the procedure for the synthesis of Example 8 by using 12A instead of 8D. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.57 (br. s., 2H), 7.06 (d, *J*=6.6 Hz, 2H), 6.19 - 5.87 (m, 1H), 4.69 (br. s., 1H), 4.13 (d, *J*=5.6 Hz, 3H), 3.21 - 3.09 (m, 2H), 2.76 (d, *J*=15.7 Hz, 3H), 2.45 - 2.37 (m, 1H), 2.01 - 1.45 (m, 18H). LC-MS, [M+H]⁺ = 471.0. hLPA1 IC₅₀ = 384 nM.

15

Example 13

3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid (single enantiomer)

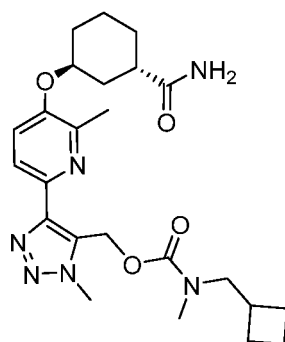


5

Example 13 was subjected to chiral SFC (Column: Chiralpak IC, 21 x 250 mm, 5 micron Mobile Phase: 40%MeOH / 60% CO₂ Flow Conditions: 45 mL/min, 150 Bar, 40°C Detector Wavelength: 254 nm Injection Details: 0.5 mL of 5 mg/mL solution in MeOH) to afford Example 13. ¹H NMR (500 MHz, CDCl₃) δ 8.11 - 7.96 (m, 1H), 7.29 (d, *J*=8.5 Hz, 1H), 5.75 (d, *J*=9.6 Hz, 2H), 4.79 (d, *J*=3.3 Hz, 1H), 4.15 (d, *J*=7.7 Hz, 3H), 3.38 - 3.11 (m, 2H), 2.93 - 2.75 (m, 3H), 2.65 - 2.51 (m, 1H), 2.25 (br. s., 1H), 2.10 - 1.47 (m, 7H). LC-MS, [M+H]⁺ = 490.4. hLPA1 IC₅₀ = 95 nM.

15 Example 14

(4-(5-(((1*S*,3*S*)-3-carbamoylcyclohexyl)oxy)-6-methylpyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate

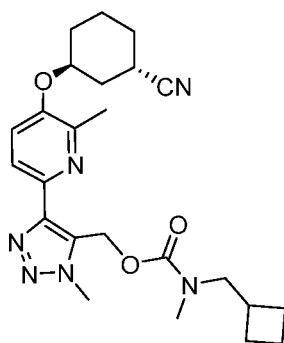


20 To a solution of Example 2 (100 mg, 0.21 mmol) and DMF (0.8 μL, 11 μmol) in CH₂Cl₂ (2 mL) was slowly added oxalyl chloride (0.21 mL, 0.42 mmol); the mixture was

stirred at rt for 30 min. The mixture was concentrated *in vacuo* to give the acid chloride. To the acid chloride in CH₂Cl₂ (1.0 mL) was added ammonia (6.36 mL of a 0.5 N solution in dioxane, 3.18 mmol). The mixture was stirred at rt for 30 min, then was concentrated *in vacuo*. The residual crude product was chromatographed (SiO₂; 12 g; A = DCM, B = EtOAc; 12 min gradient from 0% B to 100% B; flow rate = 30 mL/min) to afford the title compound (77 mg, 0.17 mmol, 89 % yield) as a white solid. LCMS, [M+H]⁺ = 471.2. ¹H NMR (500 MHz, DMSO-*d*₆) [rotamer, ratio 53:47] [major rotamer – underline; minor rotamer – *Italic*]: δ ppm 7.81 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.35 (s, 1H), 6.72 (s, 1H), 5.62 (s, 2 H), 5.59 (s, 2 H), 4.81 (br-s, 1H), 4.08 (br-s, 3H), 3.21 (br-s, 2H), 3.08 (br-s, 2H), 2.77 – 2.65 (m, 4H), 2.55 (s, 3H), 2.43 (s, 3H), 2.37 – 1.36 (m, 12H). HPLC-6: RT = 1.36 min, purity = 98%. hLPA1 IC₅₀ = 824 nM.

Example 15

(4-(5-(((1*S*,3*S*)-3-cyanocyclohexyl)oxy))-6-methylpyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate

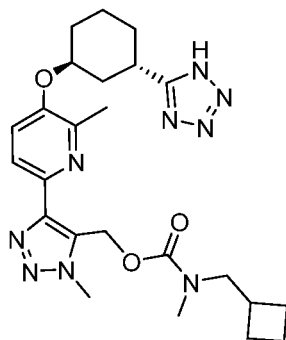


A mixture of Example 14 (90 mg, 0.19 mmol) and Burgess reagent (137 mg, 0.57 mmol) in DCM (1 mL) and THF (1 mL) was stirred at rt for 48 h, then was concentrated *in vacuo*. The residue was chromatographed (SiO₂; 12 g; A = DCM, B = EtOAc; 12 min gradient from 0% B to 100%B; flow rate = 30 mL/min) to afford the title compound (85 mg, 0.18 mmol, 95 % yield) as a white solid. LCMS, [M+H]⁺ = 453.0. ¹H NMR (500 MHz, DMSO-*d*₆) [rotamer, ratio 53:47] [major rotamer – underline; minor rotamer – *Italic*]: δ ppm 7.83 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 5.62 (s, 2 H), 5.58 (s, 2 H), 4.71 (s, 1H), 4.08 (br-s, 3H), 3.22 (br-s, 2H), 3.08 (br-s, 2H), 2.77 – 2.65 (m, 4H),

2.55 (s, 3H), 2.40 (s, 3H), 2.34 – 1.34 (m, 12H). HPLC-6: RT = 1.68 min, purity = 97%.
hLPA1 IC₅₀ = 3750 nM.

Example 16

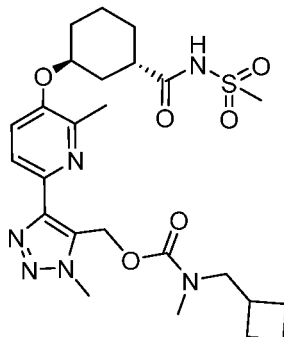
- 5 (4-(5-(((1S,3S)-3-(1H-tetrazol-5-yl)cyclohexyl)oxy)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate



- A mixture of Example 15 (69 mg, 0.15 mmol), TEA (0.32 mL, 2.3 mmol), NaN₃ (149 mg, 2.3 mmol) and HOAc (0.13 mL, 2.3 mmol) in toluene (1.0 mL) in a sealed tube
10 was stirred at 100°C for 18 h, then was cooled to rt. The mixture was diluted with EtOAc (5 mL), quenched with sat'd. aq. NaHCO₃ (3 mL). The mixture was extracted with EtOAc (5 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified by preparative LC/MS using the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase
15 A: 5:95 MeCN: water with 10 mM NH₄OAc; Mobile Phase B: 95:5 MeCN: water with 10 mM NH₄OAc; Gradient: 10-60% B over 20 min, then a 5-min hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (54 mg, 70% yield) as a white solid.
LCMS, [M+H]⁺ = 496.0. ¹H NMR (500 MHz, DMSO-*d*₆) [rotamer, ratio 53:47] [major rotamer – underline; minor rotamer– *Italic*]: δ ppm 7.82 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 5.61 (s, 2 H), 5.57 (s, 2 H), 4.88 (s, 1H), 4.07 (br-s, 3H), 3.37 (m, 1H), *3.20* (br-s, 2H), 3.06 (br-s, 2H), 2.76 – 2.65 (m, 3H), 2.54 (s, 3H), 2.44 (s, 3H), 2.37 – 1.33 (m, 12H). HPLC-6: RT = 1.50 min, purity = 96%. hLPA1 IC₅₀ = 22 nM.

- 25 Example 17

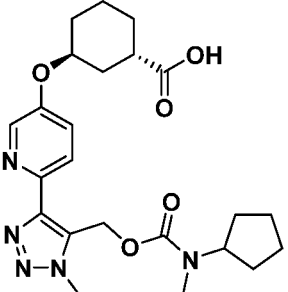
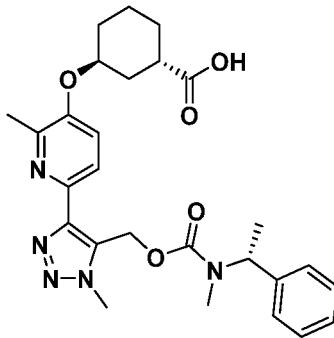
(1-methyl-4-(6-methyl-5-(((1S,3S)-3-
((methylsulfonyl)carbamoyl)cyclohexyl)oxy)pyridin-2-yl)-1H-1,2,3-triazol-5-yl)methyl
(cyclobutylmethyl)(methyl)carbamate

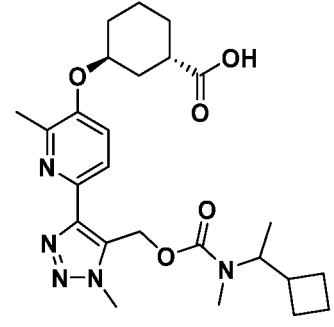
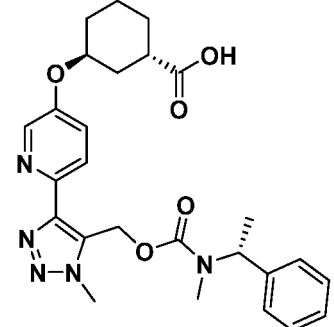


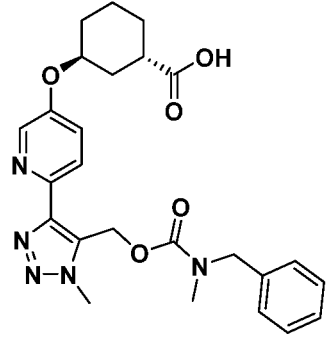
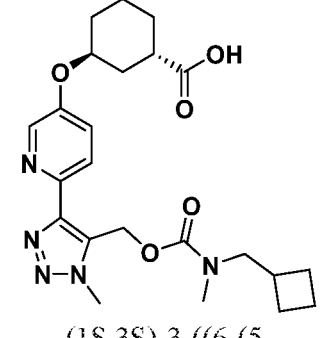
To a clear solution of Example 2 (15 mg, 0.032 mmol) and methanesulfonamide
(5 mg, 0.048 mmol) and DMAP (6 mg, 0.048 mmol) in DMF (0.2 mL) and DCM (1 mL)
was added EDC (9.4 mg, 0.048 mmol). The mixture was stirred at rt for 62 h, then was
diluted with water (2 mL) and DCM (5mL). The organic layer was washed with brine (5
mL), dried (MgSO₄) and concentrated *in vacuo* to afford a white solid, which was
purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19
x 200 mm, 5 μm particles; Mobile Phase A: 5:95 MeCN: water with 10 mM NH₄OAc;
Mobile Phase B: 95:5 MeCN: water with 10 mM NH₄OAc; Gradient: 20-70% B over 20
min, then a 3-min hold at 100% B; Flow: 20 mL/min. Fractions containing the desired
product were combined and dried via centrifugal evaporation to afford the title compound
(14 mg, 78% yield) as a white solid. LCMS, [M+H]⁺ = 549.3. ¹H NMR (500 MHz,
DMSO-*d*₆) [rotamer, ratio 53:47] [major – underlined; minor – *Italic*]: δ ppm 7.82 (d, *J* =
8.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 5.62 (s, 2 H), 5.58 (s, 2 H), 4.85 (s, 1H), 4.08 (br-s,
3H), 3.60 (m, 1H), 3.24 – 3.08 (m, 2H), 2.79 – 2.67 (m, 4H), 2.54 (s, 6H), 2.44 (s, 3H),
2.35 – 1.35 (m, 12H). HPLC-6: RT = 1.56 min, purity = 97%. hLPA1 IC₅₀ = 352 nM.

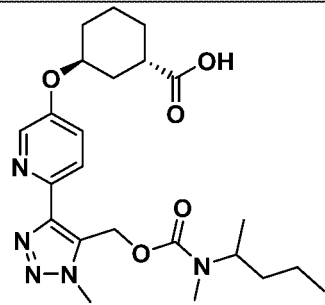
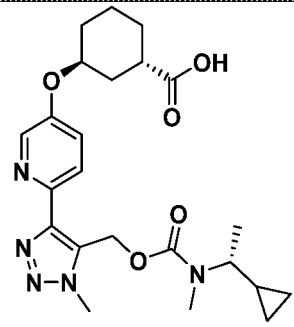
20

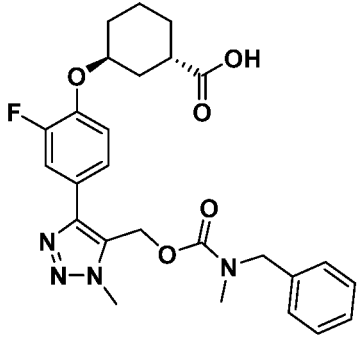
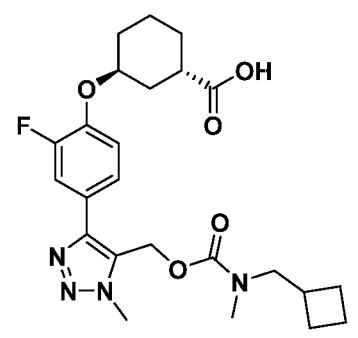
Table 1

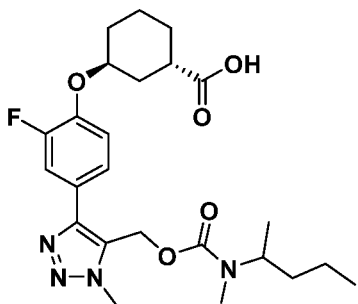
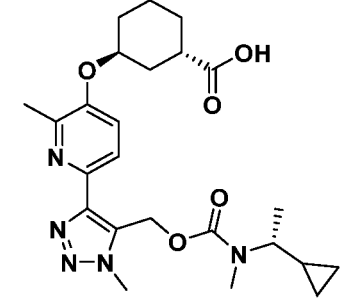
Example	Structure & Name	Analytical & Biology Data	Method
18	 (rac)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M + H]^+ = 458.3$. 1H NMR (500 MHz, CD_3CN) δ 8.26 (dd, $J=3.0, 0.6$ Hz, 1H), 8.00 - 7.96 (m, 1H), 7.38 (dd, $J=8.8, 2.8$ Hz, 1H), 5.58 (s, 2H), 4.70 (br. s., 1H), 4.03 (s, 3H), 2.79 - 2.69 (m, 1H), 2.64 (br. s., 3H), 2.01 - 1.93 (m, 2H), 1.84 - 1.73 (m, 3H), 1.71 - 1.49 (m, 8H), 1.48 - 1.36 (m, 4H) hLPA1 $IC_{50} = 21$ nM.	Example 2
19	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(R)-1-phenylethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M + H]^+ = 508.2$ 1H NMR (500 MHz, $DMSO-d_6$) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.46 (d, $J=8.6$ Hz, 1H), 7.38 - 6.97 (m, 5H), 5.68 (br s, 2H), 5.36 (br s, 1H), 5.10 (br s, 1H), 4.76 (br s, 1H), 4.14 - 3.98 (m, 2H), 3.69 (br d, $J=7.7$ Hz, 1H), 2.63 - 2.55 (m, 2H), 2.49 - 2.44 (m, 1H), 2.38 (br s, 3H), 1.99 (br d, $J=14.4$ Hz, 1H), 1.87 - 1.70 (m, 3H), 1.67 - 1.28 (m, 7H) hLPA1 $IC_{50} = 17$ nM	Example 3

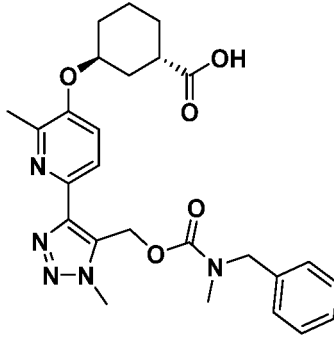
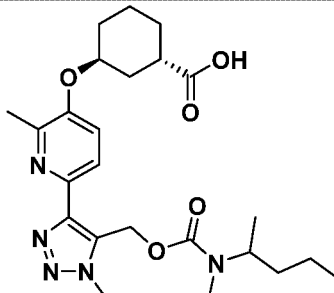
Example	Structure & Name	Analytical & Biology Data	Method
20	 (1S,3S)-3-(((6-(5-(((1-cyclobutylethyl)(methyl)carbamoyloxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M + H]^+ = 486.2$. 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.3$ Hz, 1H), 7.48 (br d, $J=8.6$ Hz, 1H), 5.85 - 5.43 (m, 2H), 4.77 (br s, 1H), 4.28 - 3.96 (m, 3H), 2.55 (s, 6H), 2.42 (br d, $J=8.6$ Hz, 3H), 1.97 (br s, 1H), 1.87 - 1.17 (m, 13H), 1.00 - 0.75 (m, 3H) hLPA1 $IC_{50} = 28$ nM.	Example 1
21	 (1S,3S)-3-(((6-(1-methyl-5-(((methyl(R)-1-phenylethyl)carbamoyloxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 494.4$ 1H NMR (500 MHz, DMSO-d_6) δ 8.43 - 8.29 (m, 1H), 8.07 - 7.94 (m, 1H), 7.66 - 7.51 (m, 1H), 7.42 - 7.04 (m, 5H), 5.78 - 5.57 (m, 2H), 5.45 - 5.03 (m, 1H), 4.87 - 4.73 (m, 1H), 4.22 - 3.95 (m, 3H), 2.74 - 2.63 (m, 1H), 2.60 - 2.56 (m, 3H), 2.00 - 1.91 (m, 1H), 1.90 - 1.71 (m, 3H), 1.70 - 1.59 (m, 2H), 1.57 - 1.33 (m, 5H) hLPA1 $IC_{50} = 21$ nM.	Example 1

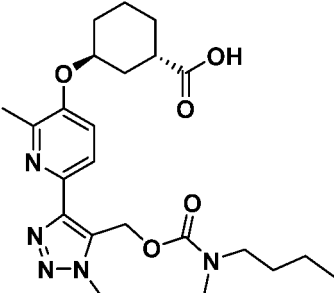
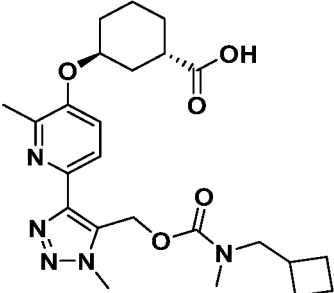
Example	Structure & Name	Analytical & Biology Data	Method
22	 (1S,3S)-3-(((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 480.1$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.34 (br. s., 1H), 8.01 (d, $J=8.5$ Hz, 1H), 7.55 (d, $J=7.0$ Hz, 1H), 7.41 - 6.96 (m, 5H), 5.77 - 5.56 (m, 2H), 4.78 (br. s., 1H), 4.50 - 4.25 (m, 2H), 4.18 - 3.91 (m, 3H), 3.50 (br. s., 1H), 2.84 - 2.62 (m, 3H), 2.02 - 1.74 (m, 4H), 1.71 - 1.45 (m, 4H) hLPA1 $\text{IC}_{50} = 18$ nM.	Example 1
23	 (1S,3S)-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 458.3$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.35 (br. s., 1H), 7.99 (d, $J=8.5$ Hz, 1H), 7.57 (d, $J=7.6$ Hz, 1H), 5.62 (d, $J=19.2$ Hz, 2H), 4.77 (br. s., 1H), 4.11 (d, $J=6.1$ Hz, 3H), 3.56 - 3.41 (m, 1H), 3.28 - 3.04 (m, 2H), 2.80 - 2.67 (m, 3H), 2.02 - 1.40 (m, 15H) hLPA1 $\text{IC}_{50} = 12$ nM.	Example 1

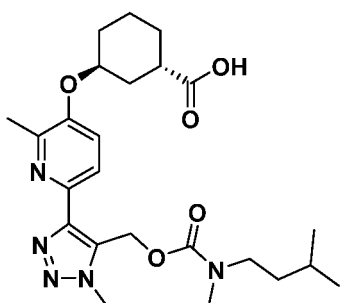
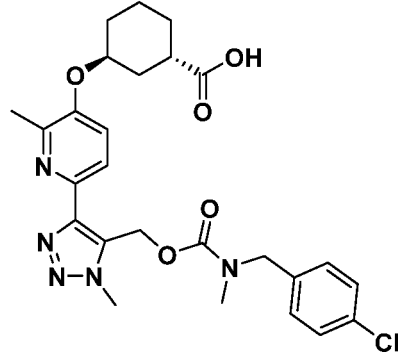
Example	Structure & Name	Analytical & Biology Data	Method
24	 (1S,3S)-3-((6-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 460.3$ 1H NMR (500 MHz, DMSO-d_6) δ 8.44 - 8.29 (m, 1H), 8.07 - 7.95 (m, 1H), 7.55 (br d, $J=7.3$ Hz, 1H), 5.73 - 5.52 (m, 2H), 4.78 (br s, 1H), 4.20 - 4.03 (m, 3H), 2.70 - 2.59 (m, 2H), 1.99 - 1.71 (m, 6H), 1.68 - 1.49 (m, 4H), 1.43 - 1.09 (m, 4H), 1.06 - 0.78 (m, 6H), 0.82 - 0.58 (m, 1H) hLPA1 $IC_{50} = 47$ nM.	Example 1
25	 (1S,3S)-3-((6-(5-((((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 458.3$ 1H NMR (400 MHz, CD_3CN) δ 8.24 (br. s., 1H), 8.12 (d, $J=8.1$ Hz, 1H), 7.93 (dd, $J=9.1, 2.5$ Hz, 1H), 5.17 (br. s., 2H), 4.80 - 4.59 (m, 1H), 3.97 (d, $J=15.8$ Hz, 3H), 3.31 - 3.07 (m, 1H), 2.72 - 2.54 (m, 4H), 2.02 - 1.76 (m, 3H), 1.70 - 1.33 (m, 5H), 1.09 - 0.87 (m, 3H), 0.84 - 0.65 (m, 1H), 0.46 - 0.13 (m, 4H) hLPA1 $IC_{50} = 20$ nM.	Example 3

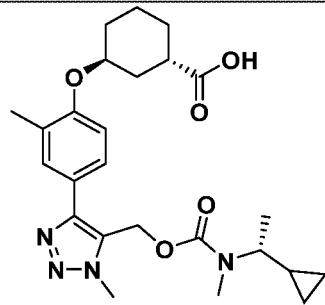
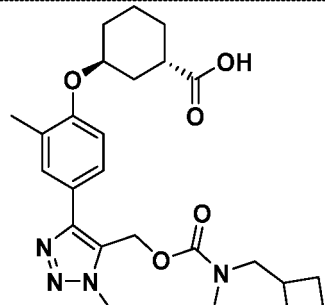
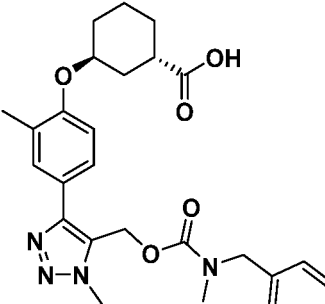
Example	Structure & Name	Analytical & Biology Data	Method
26	 (1S,3S)-3-(4-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 497.3$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.73 - 7.41 (m, 2H), 7.38 - 6.98 (m, 6H), 5.43 - 5.26 (m, 2H), 4.72 (br. s., 1H), 4.39 (d, $J=8.9$ Hz, 2H), 4.20 - 3.95 (m, 3H), 3.67 - 3.42 (m, 3H), 2.69 - 2.60 (m, 1H), 1.96 (br. s., 1H), 1.82 (t, $J=11.1$ Hz, 3H), 1.69 - 1.45 (m, 5H) hLPA1 $\text{IC}_{50} = 34$ nM.	Example 1
27	 (1S,3S)-3-(4-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 475.1$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.70 - 7.48 (m, 2H), 7.33 (t, $J=8.7$ Hz, 1H), 5.32 (d, $J=7.9$ Hz, 2H), 4.75 (br. s., 1H), 4.12 (br. s., 3H), 3.65 - 3.44 (m, 4H), 3.26 - 3.07 (m, 2H), 2.69 - 2.60 (m, 1H), 2.01 - 1.41 (m, 14H) hLPA1 $\text{IC}_{50} = 14$ nM.	Example 1

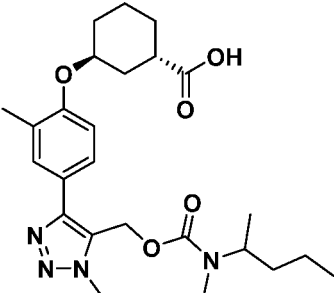
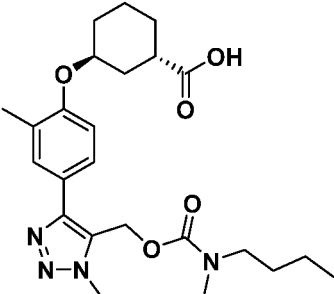
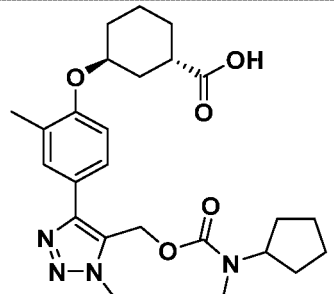
Example	Structure & Name	Analytical & Biology Data	Method
28	 (1S,3S)-3-(2-fluoro-4-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 477.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.70 - 7.43 (m, 2H), 7.32 (br t, $J=8.5$ Hz, 1H), 5.33 (br s, 2H), 4.75 (br s, 1H), 4.12 (s, 3H), 3.90 (br s, 1H), 3.52 (br d, $J=16.5$ Hz, 2H), 2.71 - 2.59 (m, 2H), 1.97 (br s, 1H), 1.88 - 1.76 (m, 3H), 1.71 - 1.45 (m, 4H), 1.43 - 1.18 (m, 2H), 1.14 - 0.91 (m, 5H), 0.82 (br t, $J=6.9$ Hz, 2H), 0.76 - 0.66 (m, 1H) hLPA1 $\text{IC}_{50} = 25$ nM.	Example 1
29	 (1S,3S)-3-((6-(5-(((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.69 (d, $J=8.2$ Hz, 1H), 7.33 (d, $J=8.2$ Hz, 1H), 5.74 - 5.34 (m, 2H), 4.64 (br. s., 1H), 3.95 (s, 3H), 3.27 (br. s., 1H), 2.67 - 2.44 (m, 4H), 2.27 (s, 3H), 1.88 (d, $J=14.0$ Hz, 1H), 1.79 - 1.59 (m, 3H), 1.56 - 1.27 (m, 4H), 1.05 - 0.63 (m, 4H), 0.44 - -0.39 (m, 4H) hLPA1 $\text{IC}_{50} = 41$ nM.	Example 3

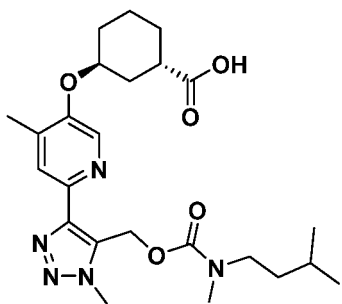
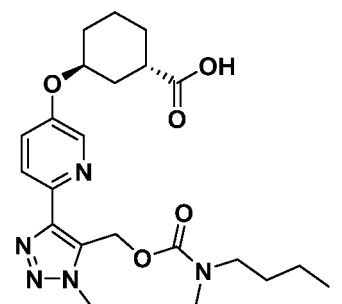
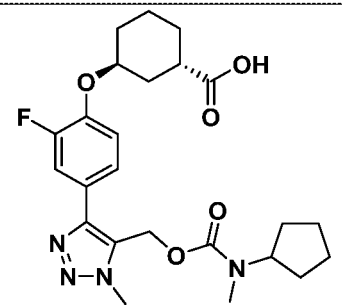
Example	Structure & Name	Analytical & Biology Data	Method
30	 (1S,3S)-3-(((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 494.3$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.86 (d, $J=8.5$ Hz, 1H), 7.49 (d, $J=8.5$ Hz, 1H), 7.39 - 6.97 (m, 5H), 5.79 - 5.63 (m, 2H), 4.79 (br. s., 1H), 4.49 - 4.26 (m, 2H), 4.17 - 3.91 (m, 3H), 2.86 - 2.69 (m, 3H), 2.68 - 2.59 (m, 1H), 2.41 (d, $J=14.3$ Hz, 3H), 2.07 - 1.98 (m, 1H), 1.92 - 1.74 (m, 3H), 1.71 - 1.45 (m, 4H) hLPA1 $\text{IC}_{50} = 16$ nM.	Example 1
31	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 474.3$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.2$ Hz, 1H), 7.48 (d, $J=7.0$ Hz, 1H), 5.66 (br. s., 2H), 4.79 (br. s., 1H), 4.10 (s, 4H), 2.63 (br. s., 3H), 2.42 (s, 3H), 2.10 - 1.97 (m, 1H), 1.91 - 1.71 (m, 4H), 1.67 - 1.10 (m, 6H), 1.06 - 0.80 (m, 4H), 0.64 (br. s., 2H) hLPA1 $\text{IC}_{50} = 36$ nM.	Example 1

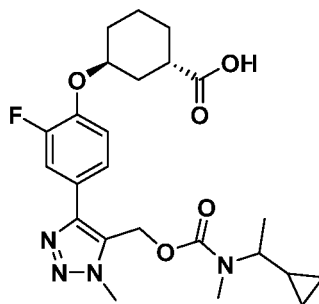
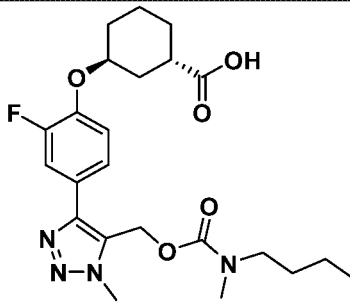
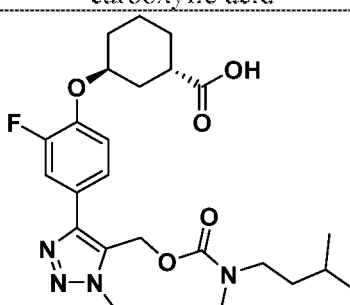
Example	Structure & Name	Analytical & Biology Data	Method
32	 (1S,3S)-3-(((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 460.3$ 1H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.64 (d, $J=15.9$ Hz, 2H), 4.79 (br. s., 1H), 4.10 (s, 3H), 3.53 - 3.32 (m, 2H), 3.23 - 3.02 (m, 1H), 2.85 - 2.69 (m, 3H), 2.42 (s, 3H), 1.81 (br. s., 3H), 1.63 (d, $J=9.8$ Hz, 6H), 1.31 - 0.96 (m, 3H), 0.66 (br. s., 3H) hLPA1 $IC_{50} = 10$ nM.	Example 1
33	 (1S,3S)-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.4$ 1H NMR (400 MHz, CD_3CN) δ 7.96 - 7.79 (m, 1H), 7.35 (d, $J=8.8$ Hz, 1H), 5.67 (br s, 2H), 4.86 - 4.62 (m, 1H), 4.19 - 3.97 (m, 4H), 3.39 - 3.01 (m, 2H), 2.88 - 2.63 (m, 4H), 2.60 - 2.29 (m, 4H), 2.18 - 2.04 (m, 1H), 1.91 - 1.44 (m, 12H), 1.29 - 1.15 (m, 1H) hLPA1 $IC_{50} = 7$ nM.	Example 1

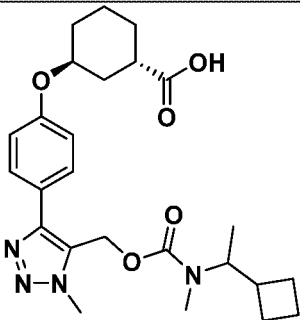
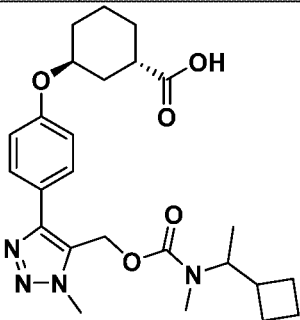
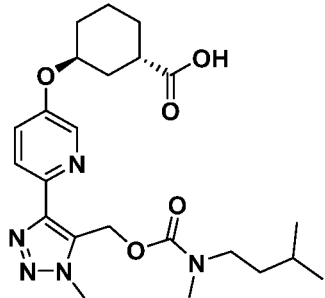
Example	Structure & Name	Analytical & Biology Data	Method
34	 (1S,3S)-3-(((6-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 474.3$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.85 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.63 (d, $J=15.3$ Hz, 2H), 4.79 (br. s., 1H), 4.10 (br. s., 3H), 3.44 (br. s., 1H), 3.22 (br. s., 1H), 3.06 (br. s., 1H), 2.84 - 2.69 (m, 3H), 2.63 (t, $J=10.4$ Hz, 1H), 2.42 (s, 3H), 2.09 - 1.97 (m, 2H), 1.92 - 1.70 (m, 2H), 1.70 - 1.42 (m, 4H), 1.40 - 1.19 (m, 2H), 1.14 (br. s., 1H), 0.88 (br. s., 3H), 0.62 (d, $J=4.6$ Hz, 3H) hLPA1 $\text{IC}_{50} = 16$ nM.	Example 1
35	 (1S,3S)-3-(((6-(5-(((4-chlorobenzyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 528.3$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.85 (d, $J=8.5$ Hz, 1H), 7.49 (d, $J=8.5$ Hz, 1H), 7.44 - 6.99 (m, 4H), 5.83 - 5.59 (m, 2H), 4.79 (br. s., 1H), 4.49 - 4.25 (m, 2H), 4.18 - 3.93 (m, 3H), 2.86 - 2.68 (m, 3H), 2.67 - 2.60 (m, 1H), 2.45 - 2.29 (m, 3H), 2.03 (d, $J=13.7$ Hz, 1H), 1.94 - 1.73 (m, 3H), 1.71 - 1.44 (m, 4H) hLPA1 $\text{IC}_{50} = 284$ nM.	Example 1

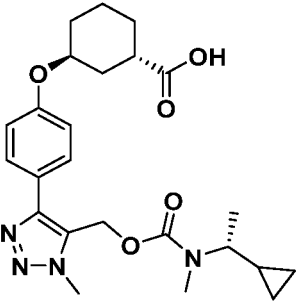
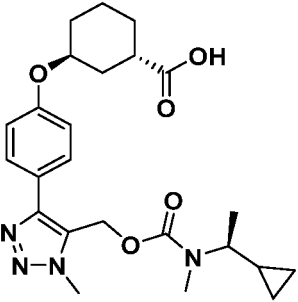
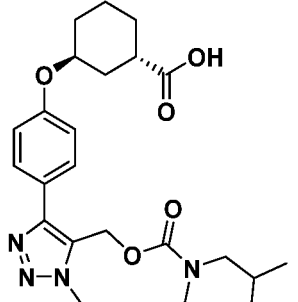
Example	Structure & Name	Analytical & Biology Data	Method
36	 (1S,3S)-3-(4-(5-((((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 471.3$ 1H NMR (400 MHz, CD_3CN) δ 7.48 - 7.31 (m, 2H), 6.87 (d, $J=8.4$ Hz, 1H), 5.11 (s, 2H), 4.62 (br. s., 1H), 3.95 (s, 3H), 2.70 - 2.56 (m, 4H), 2.13 (s, 3H), 2.02 - 1.92 (m, 1H), 1.65 - 1.33 (m, 8H), 0.99 (br. s., 3H), 0.83 - 0.68 (m, 1H), 0.37 (br. s., 1H), 0.26 - -0.22 (m, 3H) hLPA1 $IC_{50} = 6$ nM.	Example 3
37	 (1S,3S)-3-(4-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M - H]^+ = 471.3$ 1H NMR (500 MHz, $DMSO-d_6$) δ 7.66 - 7.42 (m, 2H), 7.06 (d, $J=8.5$ Hz, 1H), 5.28 (br. s., 2H), 4.74 (br. s., 1H), 4.10 (br. s., 3H), 3.48 - 3.34 (m, 2H), 2.76 (br. s., 2H), 2.65 - 2.58 (m, 1H), 2.22 (br. s., 3H), 2.02 - 1.40 (m, 15H) hLPA1 $IC_{50} = 14$ nM.	Example 1
38	 (1S,3S)-3-(4-(5-(((benzyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M - H]^+ = 493.0$ 1H NMR (500 MHz, $DMSO-d_6$) δ 7.65 - 7.39 (m, 2H), 7.37 - 6.94 (m, 7H), 5.32 (d, $J=19.5$ Hz, 2H), 4.72 (br. s., 1H), 4.39 (d, $J=13.4$ Hz, 2H), 4.18 - 3.95 (m, 3H), 2.89 - 2.70 (m, 3H), 2.62 (br. s., 1H), 2.24 - 2.10 (m, 3H), 2.00 (d, $J=11.9$ Hz, 1H), 1.90 - 1.71 (m, 3H), 1.69 - 1.39 (m, 4H) hLPA1 $IC_{50} = 32$ nM.	Example 1

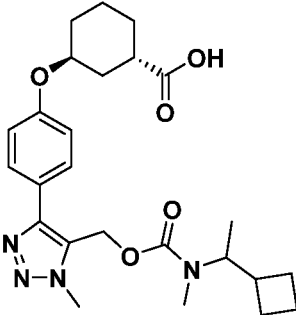
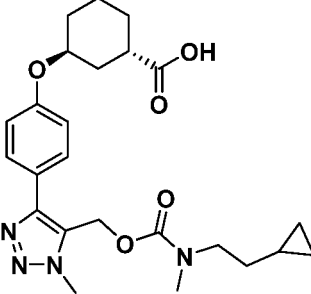
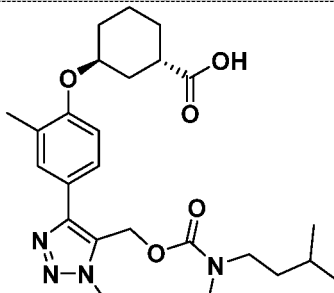
Example	Structure & Name	Analytical & Biology Data	Method
39	 (1S,3S)-3-(2-methyl-4-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 473.3$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.62 - 7.42 (m, 2H), 7.05 (d, $J=8.5$ Hz, 1H), 5.27 (br. s., 2H), 4.74 (br. s., 1H), 4.09 (s, 3H), 3.43 (br. s., 2H), 2.68 - 2.54 (m, 4H), 2.21 (s, 3H), 2.01 (d, $J=13.7$ Hz, 1H), 1.88 - 1.71 (m, 3H), 1.69 - 1.18 (m, 6H), 1.16 - 0.66 (m, 6H) hLPA1 $\text{IC}_{50} = 23$ nM.	Example 1
40	 (1S,3S)-3-(4-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 459.3$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.52 (d, $J=13.1$ Hz, 2H), 7.05 (d, $J=7.6$ Hz, 1H), 5.27 (d, $J=5.5$ Hz, 2H), 4.74 (br. s., 1H), 4.09 (s, 3H), 3.23 - 3.04 (m, 2H), 2.77 (d, $J=6.4$ Hz, 3H), 2.61 (br. s., 1H), 2.22 (s, 3H), 2.00 (d, $J=12.8$ Hz, 1H), 1.90 - 1.69 (m, 3H), 1.67 - 1.04 (m, 8H), 0.91 - 0.61 (m, 3H) hLPA1 $\text{IC}_{50} = 28$ nM.	Example 1
41	 (1S,3S)-3-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 471.3$. ^1H NMR (500 MHz, DMSO-d_6) δ 7.60 - 7.44 (m, 2H), 7.04 (d, $J=8.5$ Hz, 1H), 5.28 (s, 2H), 4.74 (br. s., 1H), 4.09 (s, 3H), 3.42 (br. s., 1H), 2.72 - 2.58 (m, 4H), 2.27 - 2.17 (m, 3H), 2.01 (d, $J=13.4$ Hz, 1H), 1.89 - 1.71 (m, 3H), 1.69 - 1.32 (m, 12H) hLPA1 $\text{IC}_{50} = 14$ nM.	Example 1

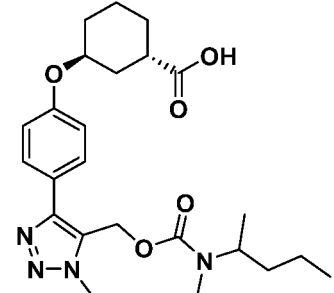
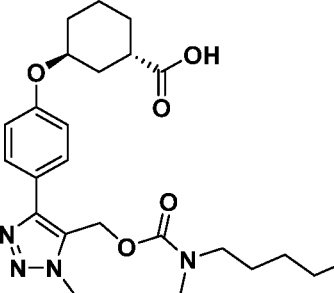
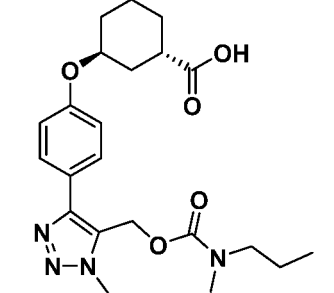
Example	Structure & Name	Analytical & Biology Data	Method
42	 (1S,3S)-3-((6-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-4-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 474.3$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.90 (s, 1H), 5.62 (d, $J=18.0$ Hz, 2H), 4.88 (br. s., 1H), 4.10 (br. s., 3H), 3.26 - 3.04 (m, 2H), 2.76 (d, $J=17.7$ Hz, 3H), 2.65 (br. s., 1H), 2.28 (s, 3H), 2.03 (d, $J=12.8$ Hz, 1H), 1.93 - 1.77 (m, 3H), 1.70 - 1.06 (m, 7H), 0.88 (d, $J=4.6$ Hz, 3H), 0.67 (d, $J=5.2$ Hz, 3H) hLPA1 $\text{IC}_{50} = 3750$ nM.	Example 1
43	 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 446.3$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, $J=2.4$ Hz, 1H), 8.00 (d, $J=8.9$ Hz, 1H), 7.55 (d, $J=8.2$ Hz, 1H), 5.62 (d, $J=18.0$ Hz, 2H), 4.79 (br. s., 1H), 4.11 (s, 3H), 3.24 - 3.04 (m, 2H), 2.82 - 2.62 (m, 4H), 1.98 (d, $J=14.0$ Hz, 1H), 1.89 - 1.73 (m, 3H), 1.72 - 1.37 (m, 5H), 1.26 (br. s., 2H), 1.05 (br. s., 1H), 0.88 (br. s., 2H), 0.69 (br. s., 2H) hLPA1 $\text{IC}_{50} = 7$ nM.	Example 1
44	 (1S,3S)-3-(4-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 475.2$. ^1H NMR (500MHz, DMSO-d_6) δ 7.61 (d, $J=12.2$ Hz, 1H), 7.53 (d, $J=8.5$ Hz, 1H), 7.35 (t, $J=8.5$ Hz, 1H), 5.34 (s, 2H), 4.75 (br. s., 1H), 4.13 (s, 3H), 3.46 - 3.30 (m, 1H), 2.73 - 2.59 (m, 4H), 2.01 - 1.30 (m, 16H) hLPA1 $\text{IC}_{50} = 6$ nM.	Example 1

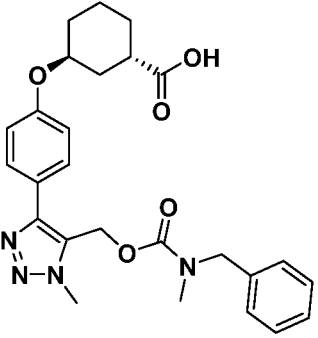
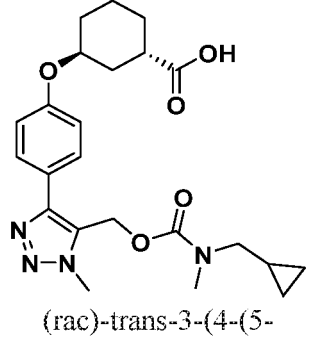
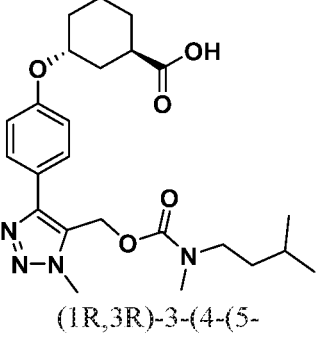
Example	Structure & Name	Analytical & Biology Data	Method
45	 (1S,3S)-3-(4-(5-(((1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 475.4$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.61 - 7.39 (m, 2H), 7.30 - 7.19 (m, 1H), 5.23 (s, 2H), 4.66 (br. s., 1H), 4.02 (s, 3H), 3.29 (br. s., 1H), 2.65 (br. s., 3H), 2.60 - 2.52 (m, 1H), 1.94 - 1.85 (m, 1H), 1.73 (d, $J=11.0$ Hz, 3H), 1.56 (d, $J=8.5$ Hz, 2H), 1.44 (br. s., 2H), 0.98 (d, $J=16.2$ Hz, 4H), 0.51 - 0.31 (m, 4H) hLPA1 $\text{IC}_{50} = 20$ nM.	Example 1
46	 (1S,3S)-3-(4-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 463.0$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.69 - 7.45 (m, 2H), 7.35 (br. s., 1H), 5.34 (br. s., 2H), 4.75 (br. s., 1H), 4.13 (s, 3H), 3.23 - 3.06 (m, 2H), 2.78 (d, $J=8.9$ Hz, 3H), 2.63 (br. s., 1H), 1.99 - 1.04 (m, 12H), 0.93 - 0.70 (m, 3H) hLPA1 $\text{IC}_{50} = 6$ nM.	Example 1
47	 (1S,3S)-3-(2-fluoro-4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 477.1$ $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 7.77 - 7.43 (m, 2H), 7.33 (br. s., 1H), 5.34 (d, $J=7.9$ Hz, 2H), 4.75 (br. s., 1H), 4.13 (br. s., 3H), 3.23 - 3.06 (m, 2H), 2.78 (d, $J=14.6$ Hz, 3H), 2.67 (br. s., 1H), 1.98 (br. s., 1H), 1.89 - 1.11 (m, 10H), 0.96 - 0.65 (m, 6H) hLPA1 $\text{IC}_{50} = 3$ nM.	Example 1

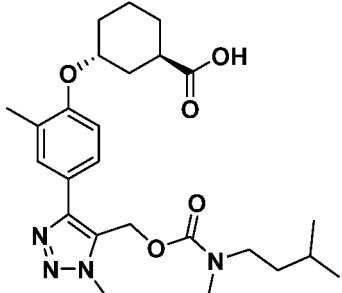
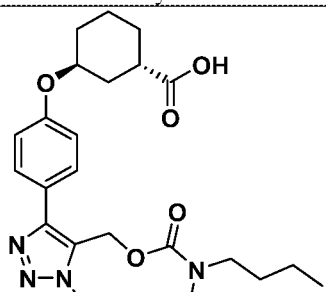
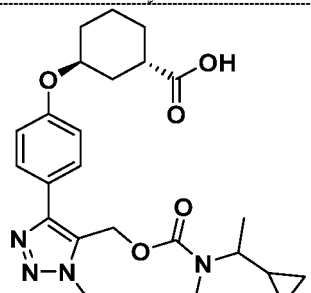
Example	Structure & Name	Analytical & Biology Data	Method
48	 (1S,3S)-3-(4-(5-((((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (isomer 1)	LCMS, $[M+H]^+ = 471.3$ 1H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 2H), 7.04 (br d, $J=7.5$ Hz, 2H), 5.32 (s, 2H), 4.72 (br s, 1H), 4.19 (br s, 3H), 2.94 (br d, $J=3.1$ Hz, 1H), 2.67 (s, 3H), 2.47 - 1.58 (m, 16H), 1.02 (br s, 3H) hLPA1 $IC_{50} = 8$ nM.	Example 1
49	 (1S,3S)-3-(4-(5-((((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (isomer 2)	LCMS, $[M+H]^+ = 471.3$ 1H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.62 (m, 2H), 7.03 (br d, $J=3.3$ Hz, 2H), 5.32 (br d, $J=2.9$ Hz, 2H), 4.87 - 4.56 (m, 1H), 4.19 (br s, 3H), 3.07 - 2.86 (m, 1H), 2.67 (br s, 3H), 2.49 - 1.49 (m, 16H), 1.05 - 0.93 (m, 3H) hLPA1 $IC_{50} = 14$ nM.	Example 1
50	 (1S,3S)-3-((6-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 460.2$ 1H NMR (500 MHz, $DMSO-d_6$) δ 8.34 (br. s., 1H), 8.09 - 7.93 (m, 1H), 7.55 (d, $J=7.9$ Hz, 1H), 5.62 (d, $J=16.8$ Hz, 2H), 4.78 (br. s., 1H), 4.11 (br. s., 3H), 3.29 - 3.00 (m, 2H), 2.76 (d, $J=17.7$ Hz, 3H), 2.64 (br. s., 1H), 1.97 - 1.45 (m, 8H), 1.40 - 1.14 (m, 2H), 0.88 (d, $J=4.9$ Hz, 3H), 0.67 (d, $J=5.2$ Hz, 3H) hLPA1 $IC_{50} = 12$ nM.	Example 1

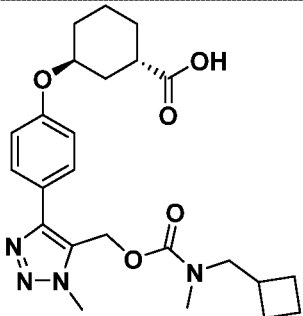
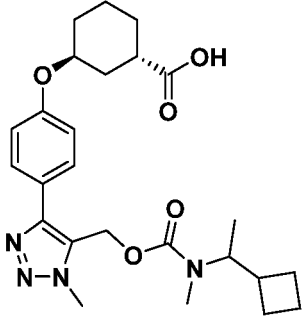
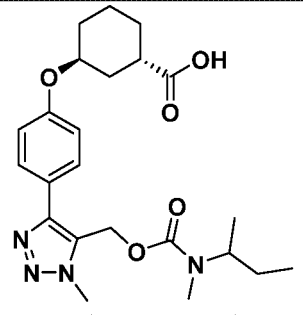
Example	Structure & Name	Analytical & Biology Data	Method
51	 (1S,3S)-3-(4-(5-((((R)-1-cyclopropylethyl)(methyl)carbamoyloxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 457.3$ ^1H NMR (400 MHz, CD_3CN) δ 7.64 - 7.44 (m, 2H), 6.89 (d, $J=8.8$ Hz, 2H), 5.10 (s, 2H), 4.61 - 4.49 (m, 1H), 3.94 (s, 3H), 2.70 - 2.52 (m, 4H), 1.96 - 1.85 (m, 1H), 1.75 - 1.35 (m, 8H), 0.97 (br. s., 3H), 0.75 (br. s., 1H), 0.44 - 0.25 (m, 4H) hLPA1 $\text{IC}_{50} = 24$ nM. <i>In vivo</i> acute histamine assay : -73% histamine at a 3 mg/kg dose of Example 51	Example 1
52	 (1S,3S)-3-(4-(5-((((S)-1-cyclopropylethyl)(methyl)carbamoyloxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 457.2$ ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.54 (d, $J=8.2$ Hz, 2H), 6.96 (d, $J=8.2$ Hz, 2H), 5.18 (br. s., 2H), 4.59 (br. s., 1H), 3.99 (s, 3H), 2.62 (br. s., 3H), 2.51 (br. s., 1H), 1.74 - 1.31 (m, 8H), 1.06 - 0.90 (m, 3H), 0.87 - 0.71 (m, 1H), 0.43 - -0.30 (m, 4H) hLPA1 $\text{IC}_{50} = 197$ nM.	Example 3
53	 (1S,3S)-3-(4-(5-(((isobutyl(methyl)carbamoyloxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 445.2$ ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.68 (br. s., 2H), 7.08 (d, $J=8.2$ Hz, 2H), 5.31 (s, 2H), 4.72 (br. s., 1H), 4.12 (s, 3H), 3.08 - 2.93 (m, 2H), 2.80 (d, $J=15.3$ Hz, 3H), 2.67 (br. s., 1H), 2.03 - 1.48 (m, 9H), 0.88 - 0.64 (m, 6H) hLPA1 $\text{IC}_{50} = 440$ nM.	Example 1

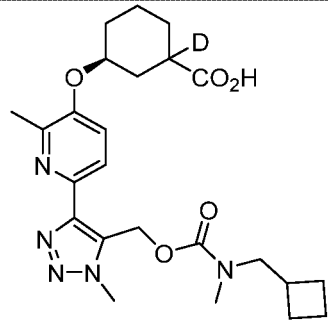
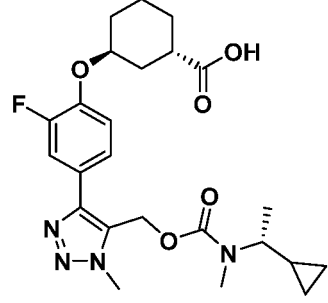
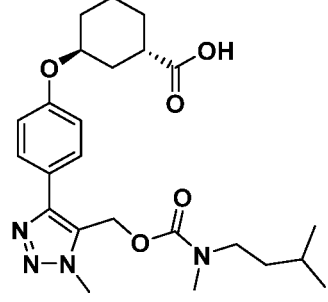
Example	Structure & Name	Analytical & Biology Data	Method
54	 (1S,3S)-3-(4-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 471.2$ 1H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, $J=9.4$ Hz, 2H), 6.93 (d, $J=7.5$ Hz, 2H), 5.21 (s, 2H), 4.61 (br. s., 1H), 4.10 (d, $J=2.2$ Hz, 4H), 3.84 (dd, $J=10.3, 6.6$ Hz, 1H), 2.98 - 2.76 (m, 1H), 2.69 - 2.53 (m, 3H), 2.34 - 2.19 (m, 1H), 2.08 (d, $J=13.9$ Hz, 1H), 2.00 - 1.40 (m, 12H), 0.90 (dd, $J=17.7, 6.7$ Hz, 3H) hLPA1 $IC_{50} = 19$ nM.	Example 2
55	 (rac)-trans-3-(4-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 457.2$ 1H NMR (500 MHz, $DMSO-d_6$) δ 7.80 (br. s., 2H), 7.20 (d, $J=7.6$ Hz, 2H), 5.43 (br. s., 2H), 4.83 (br. s., 1H), 4.24 (s, 3H), 3.54 - 3.30 (m, 3H), 2.93 (d, $J=9.2$ Hz, 3H), 2.79 (br. s., 1H), 2.17 - 1.30 (m, 10H), 0.76 - 0.06 (m, 4H) hLPA1 $IC_{50} = 41$ nM.	Example 3
56	 (1S,3S)-3-(4-(5-(((isopentyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 473.2$ 1H NMR (400 MHz, CD_3CN) δ 7.61 (d, $J=15.2$ Hz, 2H), 7.05 (br. s., 1H), 5.33 (br. s., 2H), 4.79 (br. s., 1H), 4.14 (s, 3H), 3.35 - 3.13 (m, 2H), 2.91 - 2.72 (m, 4H), 2.36 - 2.26 (m, 3H), 2.14 (d, $J=13.4$ Hz, 1H), 1.89 - 1.26 (m, 10H), 1.02 - 0.68 (m, 6H) hLPA1 $IC_{50} = 3$ nM.	Example 2

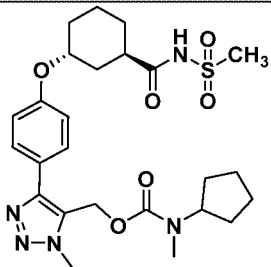
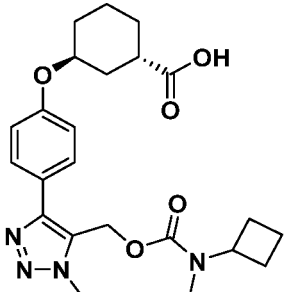
Example	Structure & Name	Analytical & Biology Data	Method
57	 trans-3-(4-(1-methyl-5-(((methyl(pentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 459.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.67 (t, $J=9.6$ Hz, 2H), 7.16 - 6.98 (m, 2H), 5.31 (s, 2H), 4.72 (br. s., 1H), 4.12 (s, 3H), 2.66 (d, $J=10.1$ Hz, 1H), 2.04 - 1.47 (m, 10H), 1.46 - 1.28 (m, 3H), 1.19 - 0.65 (m, 9H) hLPA1 $IC_{50} = 142$ nM.	Example 2
58	 (rac)-trans-3-(4-(1-methyl-5-(((methyl(pentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 459.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.70 (d, $J=8.2$ Hz, 2H), 7.08 (d, $J=7.6$ Hz, 2H), 5.31 (br. s., 2H), 4.72 (br. s., 1H), 4.12 (s, 3H), 3.23 - 3.08 (m, 2H), 2.79 (d, $J=13.7$ Hz, 3H), 2.67 (br. s., 1H), 2.03 - 1.01 (m, 14H), 0.93 - 0.69 (m, 3H) hLPA1 $IC_{50} = 250$ nM.	Example 2
59	 (rac)-trans-3-(4-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 431.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.68 (br. s., 2H), 7.09 (d, $J=8.5$ Hz, 2H), 5.31 (s, 2H), 4.72 (br. s., 1H), 4.12 (s, 3H), 3.20 - 3.07 (m, 2H), 2.80 (d, $J=9.8$ Hz, 3H), 2.67 (br. s., 1H), 2.05 - 1.31 (m, 10H), 0.84 - 0.65 (m, 3H) hLPA1 $IC_{50} = 1880$ nM.	Example 2

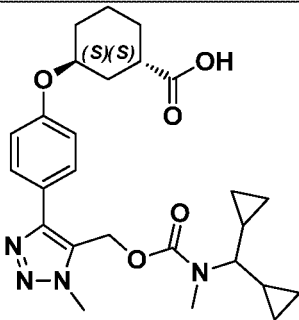
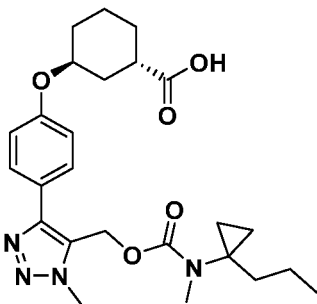
Example	Structure & Name	Analytical & Biology Data	Method
60	 (rac)-trans-3-(4-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 479.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.80 - 7.55 (m, 2H), 7.44 - 6.96 (m, 7H), 5.48 - 5.16 (m, 2H), 4.70 (br. s., 1H), 4.41 (d, $J=12.8$ Hz, 2H), 4.21 - 3.94 (m, 3H), 2.90 - 2.73 (m, 3H), 2.70 - 2.61 (m, 1H), 2.04 - 1.48 (m, 8H) hLPA1 $IC_{50} = 130$ nM.	Example 2
61	 (rac)-trans-3-(4-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 443.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.66 - 7.46 (m, 2H), 7.08 - 6.86 (m, 2H), 5.28 - 5.11 (m, 2H), 4.68 - 4.59 (m, 1H), 4.10 - 3.94 (m, 3H), 3.08 - 2.91 (m, 3H), 2.85 - 2.71 (m, 3H), 2.65 - 2.54 (m, 1H), 1.97 - 1.39 (m, 8H), 0.96 - 0.67 (m, 1H), 0.46 - 0.22 (m, 2H), 0.16 to -0.08 (m, 2H) hLPA1 $IC_{50} = 273$ nM.	Example 2
62	 (1R,3R)-3-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 459.2$ 1H NMR (400 MHz, CD_3CN) δ 7.80 - 7.65 (m, 2H), 7.12 - 6.96 (m, 2H), 5.35 - 5.24 (m, 2H), 4.78 - 4.70 (m, 1H), 5.07 - 4.33 (m, 1H), 4.20 - 4.06 (m, 3H), 3.37 - 3.14 (m, 2H), 2.93 - 2.72 (m, 4H), 2.13 - 2.02 (m, 1H), 1.92 - 1.22 (m, 10H), 0.99 - 0.74 (m, 6H) hLPA1 $IC_{50} = 1290$ nM.	Example 2

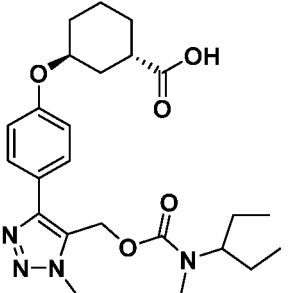
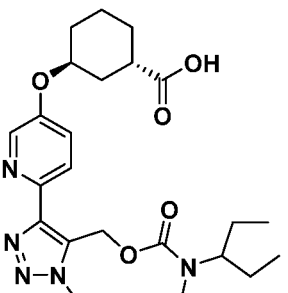
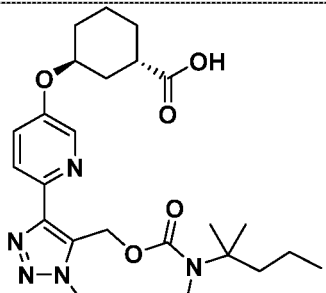
Example	Structure & Name	Analytical & Biology Data	Method
63	 (1R,3R)-3-(4-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylphenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 473.2$ 1H NMR (400 MHz, CD_3CN) δ 7.65 - 7.46 (m, 2H), 7.04 (d, $J=8.4$ Hz, 1H), 5.29 (br. s., 2H), 4.78 (br. s., 1H), 4.13 (s, 3H), 3.30 - 3.19 (m, 2H), 2.88 - 2.74 (m, 4H), 2.30 (s, 3H), 2.18 - 2.09 (m, 1H), 1.80 - 1.25 (m, 11H), 0.96 - 0.70 (m, 6H) hLPA1 $IC_{50} = 701$ nM.	Example 2
64	 (rac)-trans-3-(4-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 445.2$ (500 MHz, $DMSO-d_6$) δ 7.76 - 7.57 (m, 2H), 7.17 - 6.94 (m, 2H), 5.42 - 5.23 (m, 2H), 4.77 - 4.62 (m, 1H), 4.19 - 4.04 (m, 3H), 3.28 - 3.06 (m, 2H), 2.88 - 2.75 (m, 3H), 2.71 - 2.59 (m, 1H), 2.01 - 1.03 (m, 13H), 0.92 - 0.68 (m, 3H) hLPA1 $IC_{50} = 32$ nM.	Example 1
65	 trans-3-(4-(5-(((1-cyclopropylethyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 457.2$ 1H NMR (500 MHz, $DMSO-d_6$) δ 7.54 (d, $J=8.5$ Hz, 2H), 6.96 (d, $J=8.2$ Hz, 2H), 5.19 (br. s., 2H), 4.60 (br. s., 1H), 3.99 (s, 3H), 2.63 (br. s., 4H), 2.60 - 2.51 (m, 1H), 1.95 - 1.34 (m, 8H), 1.06 - 0.71 (m, 4H), 0.47 - 0.29 (m, 4H) hLPA1 $IC_{50} = 80$ nM.	Example 1

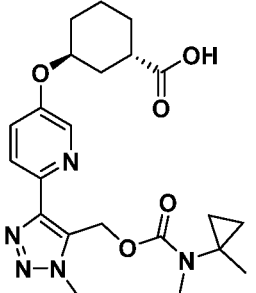
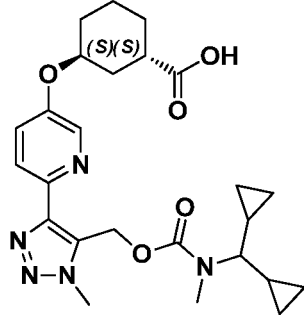
Example	Structure & Name	Analytical & Biology Data	Method
66	 (rac)-trans-3-(4-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 457.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.70 (d, $J=7.9$ Hz, 2H), 7.09 (d, $J=8.5$ Hz, 2H), 5.31 (br. s., 2H), 4.72 (br. s., 1H), 4.12 (br. s., 3H), 3.31 - 3.13 (m, 2H), 2.78 (d, $J=11.0$ Hz, 3H), 2.67 (br. s., 1H), 2.03 - 1.45 (m, 15H) hLPA1 $IC_{50} = 68$ nM.	Example 1
67	 trans-3-(4-(5-(((1-cyclobutylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 471.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.81 - 7.58 (m, 2H), 7.12 - 7.03 (m, 2H), 5.43 - 5.17 (m, 2H), 4.71 (br. s., 1H), 4.12 (d, $J=12.2$ Hz, 3H), 4.06 - 3.74 (m, 1H), 3.00 (s, 3H), 2.66 (br. s., 1H), 2.03 - 1.44 (m, 15H), 0.94 - 0.81 (m, 3H) hLPA1 $IC_{50} = 109$ nM.	Example 1
68	 (trans)-3-(4-(5-(((sec-butyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 445.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.75 - 7.60 (m, 2H), 7.08 (d, $J=8.9$ Hz, 2H), 5.31 (s, 2H), 4.71 (br. s., 1H), 4.11 (s, 3H), 4.05 - 3.73 (m, 1H), 2.73 - 2.57 (m, 4H), 2.02 - 1.27 (m, 10H), 1.08 - 0.92 (m, 3H), 0.76 - 0.57 (m, 3H) hLPA1 $IC_{50} = 320$ nM.	Example 1

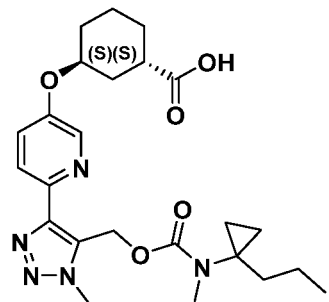
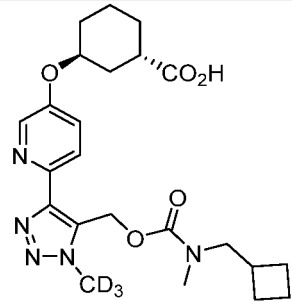
Example	Structure & Name	Analytical & Biology Data	Method
69	 (3S)-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic-1-d acid (homochiral)	LCMS, $[M+H]^+ = 473.0$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.5$ Hz, 1H), 7.52 (d, $J=8.6$ Hz, 1H), 5.62 (d, $J=19.4$ Hz, 2H), 4.09 (d, $J=7.2$ Hz, 3H), 3.33 - 3.04 (m, 2H), 2.82 - 2.67 (m, 3H), 2.36 (br. s., 3H), 2.45 - 2.16 (m, 1H), 2.08 - 1.15 (m, 14H) hLPA1 $\text{IC}_{50} = 57$ nM.	Example 2 (using intermediate 2)
70	 (1S,3S)-3-(4-(5-(((R)-1-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-fluorophenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 475.3$ ^1H NMR (400MHz, CDCl_3) δ 7.51 - 7.32 (m, 2H), 7.03 (t, $J=8.5$ Hz, 1H), 5.28 - 5.12 (m, 2H), 4.62 (br. s., 1H), 4.11 (s, 3H), 3.41 (d, $J=9.0$ Hz, 1H), 3.19 (br. s., 1H), 2.98 - 2.69 (m, 4H), 2.11 (d, $J=13.6$ Hz, 1H), 2.01 - 1.67 (m, 4H), 1.65 - 1.49 (m, 3H), 1.11 (d, $J=6.6$ Hz, 3H), 0.78 (br. s., 1H), 0.57 - -0.15 (m, 3H) hLPA1 $\text{IC}_{50} = 10$ nM.	Example 1
71	 (rac)-trans-3-(4-(5-(((isopentyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 459.2$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.88 - 7.56 (m, 2H), 7.08 (br. s., 2H), 5.31 (br. s., 2H), 4.71 (br. s., 1H), 4.12 (s, 3H), 3.29 - 3.05 (m, 2H), 2.79 (d, $J=17.1$ Hz, 3H), 2.70 - 2.60 (m, 1H), 2.05 - 1.19 (m, 11H), 0.93 - 0.69 (m, 6H) hLPA1 $\text{IC}_{50} = 13$ nM.	Example 2

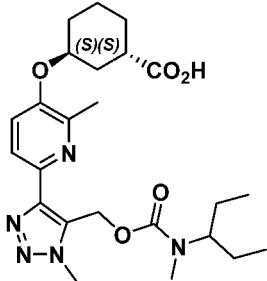
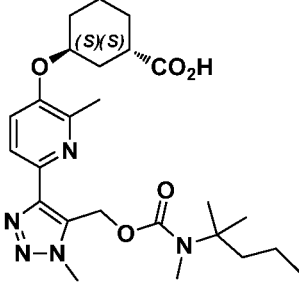
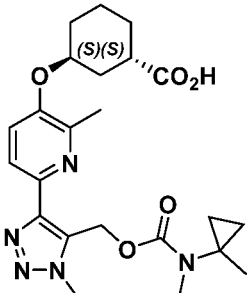
Example	Structure & Name	Analytical & Biology Data	Method
72	 (1-Methyl-4-(4-(((1R,3R)-3-((methylsulfonyl)carbamoyl)cyclohexyl)oxy)phenyl)-1H-1,2,3-triazol-5-yl)methyl cyclopentyl (methyl)carbamate	LCMS, $[M+H]^+ = 534.4$ 1H NMR (400 MHz, CD_3OD) δ 7.67 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 5.37 (s, 2H), 4.20 (s, 3H), 3.20 (s, 3H), 2.78 - 2.89 (m, 5H), 1.59 - 2.10 (m, 17H). hLPA1 $IC_{50} = 2780$ nM.	Example 7
73	 (1S,3S)-3-(4-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 443.5$ 1H NMR (400 MHz, CD_3OD) δ 7.64 (d, $J = 8.00$ Hz, 2H), 7.08 (d, $J = 8.00$ Hz, 2H), 5.33 (s, 2H), 4.72 - 4.74 (m, 1H), 4.18 (s, 3H), 2.78 - 2.84 (m, 4H), 2.08 - 2.14 (m, 5H), 1.82 - 1.93 (m, 3H), 1.41 - 1.79 (m, 7H). hLPA1 $IC_{50} = 62$ nM.	Example 10

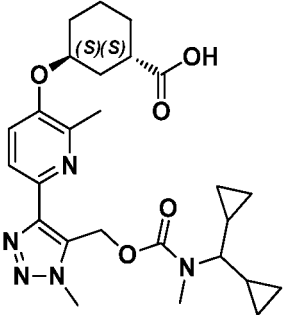
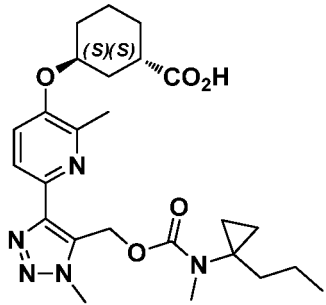
Example	Structure & Name	Analytical & Biology Data	Method
74	 (1S,3S)-3-(4-(5-(((Dicyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexanecarboxylic acid	LCMS, $[M+H]^+ = 483.2$ 1H NMR (400 MHz, CD_3OD) δ 7.66 (d, $J = 8.80$ Hz, 2H), 7.09 (d, $J = 8.80$ Hz, 2H), 5.36 (s, 2H), 4.83 - 4.89 (m, 1H), 4.19 (s, 3H), 2.90 - 2.97 (m, 3H), 2.70 - 2.87 (m, 2H), 2.08 - 2.15 (m, 1H), 1.90 - 1.99 (m, 3H), 1.62 - 1.74 (m, 4H), 1.05 - 1.09 (m, 2H), 0.50 - 0.70 (m, 2H), 0.12 - 0.43 (m, 6H). hLPA1 $IC_{50} = 100$ nM.	Example 3
75	 (1S,3S)-3-(4-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 471.2$ 1H NMR (400 MHz, CD_3OD) δ 7.70 - 7.80 (m, 1H), 7.60 - 7.70 (m, 1H), 7.08 (m, 2H), 5.30 - 5.39 (m, 2H), 4.81 - 4.83 (m, 1H), 4.18 - 4.21 (m, 3H), 2.89 (s, 3H), 2.79 - 2.82 (m, 1H), 2.06 - 2.12 (m, 1H), 1.80 - 2.00 (m, 3H), 1.60 - 1.80 (m, 4H), 1.20 - 1.50 (m, 4H), 0.80 - 0.90 (m, 2H), 0.70 - 0.80 (m, 3H), 0.60 - 0.70 (m, 2H). hLPA1 $IC_{50} = 20$ nM.	Example 3

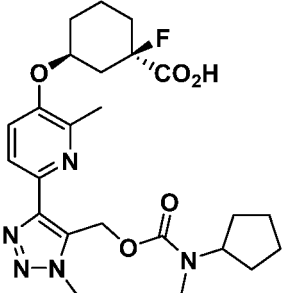
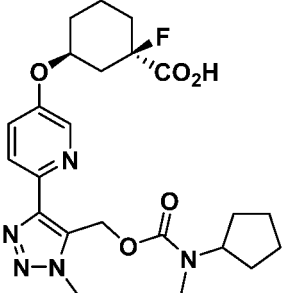
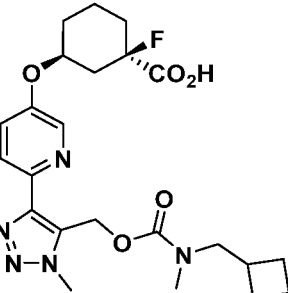
Example	Structure & Name	Analytical & Biology Data	Method
76	 (1S,3S)-3-(4-(1-methyl-5-(((methyl(pentan-3-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 459.2$ 1H NMR (400 MHz, CD_3OD) δ 7.60 - 7.70 (m, 2H), 7.10 - 7.00 (m, 2H), 5.37 (s, 2H), 4.70 - 4.80 (m, 1H), 4.18 (s, 3H), 2.75 - 2.85 (m, 1H), 2.60 - 2.70 (m, 3H), 2.08 - 2.15 (m, 1H), 1.90 - 2.00 (m, 3H), 1.60 - 1.75 (m, 5H), 1.40 - 1.50 (m, 4H), 0.71 - 0.81 (m, 6H). hLPA1 $IC_{50} = 47$ nM.	Example 3
77	 (1S,3S)-3-((6-(1-methyl-5-(((methyl(pentan-3-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 460.4$ 1H NMR (400 MHz, CD_3OD) δ 8.30 - 8.46 (m, 1H), 7.90 - 7.97 (m, 1H), 7.51 - 7.65 (m, 1H), 5.70 (d, $J = 10.8$ Hz, 1H), 4.50 - 4.60 (m, 1H), 4.20 (s, 3H), 3.62 - 3.93 (m, 1H), 2.71 - 2.82 (m, 1H), 2.60 - 2.70 (m, 3H), 1.82 - 2.10 (m, 4H), 1.57 - 1.79 (m, 4H), 1.36 - 1.49 (m, 5H), 0.82 (t, $J = 7.2$ Hz, 3H), 0.67 (t, $J = 7.6$ Hz, 3H). hLPA1 $IC_{50} = 242$ nM.	Example 1
78	 (1S,3S)-3-((6-(1-methyl-5-(((methyl(2-methylpentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 474.4$ 1H NMR (400 MHz, CD_3OD) δ 8.30 - 8.50 (m, 1H), 7.94 - 8.05 (m, 1H), 7.53 (d, $J = 8.40$ Hz, 1H), 5.66 (s, 2H), 4.82 - 4.86 (m, 1H), 4.20 (s, 3H), 2.75 - 2.90 (m, 4H), 1.90 - 2.20 (m, 4H), 1.60 - 1.90 (m, 6H), 1.31 (s, 6H), 1.15 - 1.21 (m, 2H), 0.80 (t, $J = 6.40$ Hz, 3H). hLPA1 $IC_{50} = 27$ nM.	Example 1

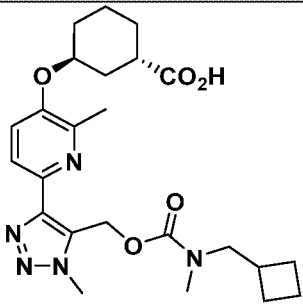
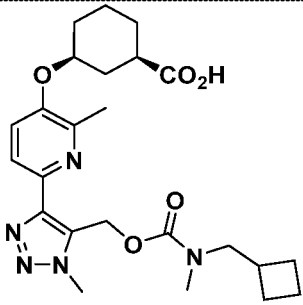
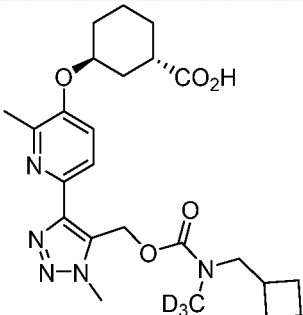
Example	Structure & Name	Analytical & Biology Data	Method
79	 (1S,3S)-3-(((6-(1-methyl-5-((methyl(1-methylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 444.2$ ^1H NMR (400 MHz, CD_3OD) δ 8.35 - 8.40 (m, 1H), 7.97 (d, $J = 9.20$ Hz, 1H), 7.53 (dd, $J = 8.8$ & 2.8 Hz, 1H), 5.70 (s, 2H), 4.80 - 4.85 (m, 1H), 4.21 (d, $J = 16.00$ Hz, 3H), 2.81-2.87 (m, 4H), 1.91 - 2.11 (m, 4H), 1.63 - 1.87 (m, 4H), 1.12 (s, 3H), 0.56 - 0.87 (m, 4H). hLPA1 $\text{IC}_{50} = 45$ nM.	Example 1
80	 (1S,3S)-3-(((5-(((Dicyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexanecarboxylic acid	LCMS, $[M+H]^+ = 484.4$ ^1H NMR (400 MHz, CD_3OD) δ 8.32-8.40 (m, 1H), 7.97-8.04 (m, 1H), 7.53 (d, $J = 8.00$ Hz, 1H), 5.60 - 5.80 (m, 2H), 4.82-4.87 (m, 1H), 4.19 (s, 3H), 2.91 (d, $J = 14.80$ Hz, 3H), 2.79-2.81 (m, 2H), 2.40 - 2.50 (m, 1H), 1.91-2.10 (m, 4H), 1.63-1.79 (m, 4H), 0.99-1.07 (m, 2H), 0.51-0.68 (m, 2H), 0.13-0.41 (m, 5H). hLPA1 $\text{IC}_{50} = 60$ nM.	Example 3

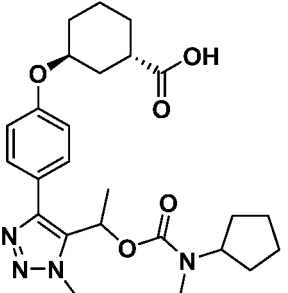
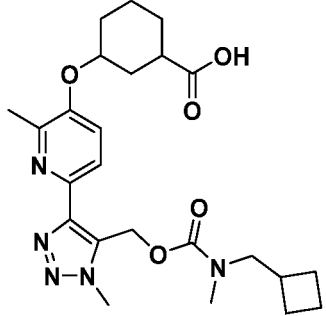
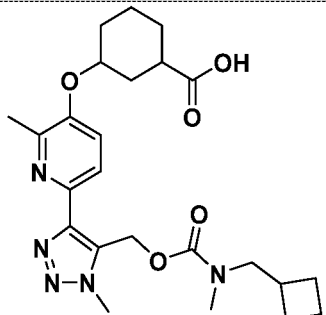
Example	Structure & Name	Analytical & Biology Data	Method
81	 (1S,3S)-3-((6-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.2$ 1H NMR (400 MHz, CD_3OD) δ 8.31-8.39 (m, 1H), 7.94-8.02 (m, 1H), 7.52 (d, $J = 8.40$ Hz, 1H), 5.67 - 5.70 (m, 2H), 4.81 - 4.89 (m, 1H), 4.40 - 4.50 (m, 1H), 4.20 (d, $J = 16.40$ Hz, 3H), 2.72 - 2.87 (m, 3H), 1.85 - 2.10 (m, 4H), 1.60 - 1.73 (m, 4H), 1.10 - 1.40 (m, 4H), 0.84 - 0.90 (m, 2H), 0.65 - 0.76 (m, 4H), 0.56 - 0.59 (m, 1H). hLPA1 $IC_{50} = 61$ nM.	Example 3
82	 (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-(methyl-d3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 460.9$ 1H NMR (500 MHz, $DMSO-d_6$) δ 8.35 (br. s., 1H), 7.99 (d, $J=8.7$ Hz, 1H), 7.54 (d, $J=6.6$ Hz, 1H), 5.85 - 5.40 (m, 2H), 4.78 (br. s., 1H), 3.59 - 2.83 (m, 2H), 2.79 - 2.60 (m, 4H), 2.03 - 1.36 (m, 14H), 1.16 (t, $J=7.2$ Hz, 1H) hLPA1 $IC_{50} = 28$ nM.	Example 4

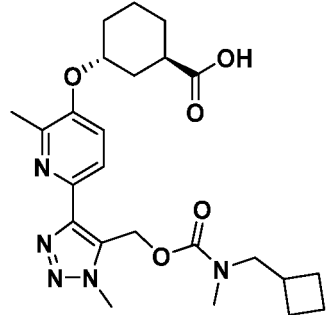
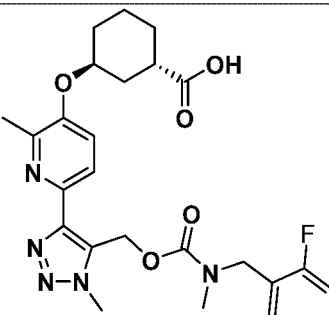
Example	Structure & Name	Analytical & Biology Data	Method
83	 (1S,3S)-3-((2-Methyl-6-(1-methyl-5-(((methyl(pentan-3-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexanecarboxylic acid	LCMS, $[M+H]^+ = 474.4$ 1H NMR (400 MHz, CD_3OD) δ 7.68 (d, $J = 8.0$ Hz, 1H), 7.35 - 7.40 (m, 1H), 5.55 - 5.65 (m, 2H), 4.20 - 4.30 (m, 1H), 4.07 (s, 3H), 3.75 - 3.90 (m, 1H), 3.55 - 3.70 (m, 1H), 2.50 - 2.70 (m, 3H), 2.20 - 2.40 (m, 3H), 1.80 - 2.10 (m, 3H), 1.94 (s, 3H), 1.55 - 1.84 (m, 3H), 1.10 - 1.40 (m, 3H), 0.70 (t, $J = 7.6$ Hz, 3H), 0.55 (t, $J = 7.2$ Hz, 3H). hLPA1 $IC_{50} = 92$ nM.	Example 2
84	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(2-methylpentan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexanecarboxylic acid	LCMS, $[M+H]^+ = 488.2$ 1H NMR (400 MHz, CD_3OD) δ 7.70 (d, $J = 8.4$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 5.56 (s, 2H), 4.07 (s, 3H), 2.74 (s, 3H), 2.62 - 2.69 (m, 1H), 2.40 (s, 3H), 1.98 - 2.05 (m, 1H), 1.80 - 1.90 (m, 3H), 1.45 - 1.70 (m, 5H), 1.20 (s, 6H), 1.01 - 1.10 (m, 3H), 0.71 - 0.79 (m, 1H), 0.60 - 0.70 (m, 3H). hLPA1 $IC_{50} = 69$ nM.	Example 1
85	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-methylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 458.2$ 1H NMR (400 MHz, CD_3OD) δ 7.81 (d, $J = 8$ Hz, 1H), 7.44 (d, $J = 8$ Hz, 1H), 5.71 (s, 2H), 4.79 - 4.81 (m, 1H), 4.13 - 4.26 (m, 3H), 2.74 - 2.88 (m, 4H), 2.51 (s, 3H), 2.06 - 2.18 (m, 1H), 1.86 - 1.96 (m, 3H), 1.62 - 1.83 (m, 4H), 1.11 (br. s., 3H), 0.43 - 0.85 (m, 4H). hLPA1 $IC_{50} = 58$ nM.	Example 1

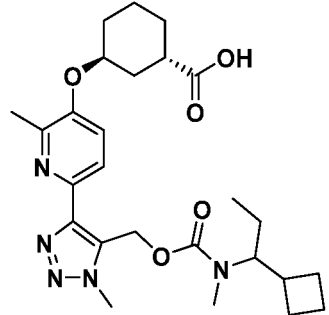
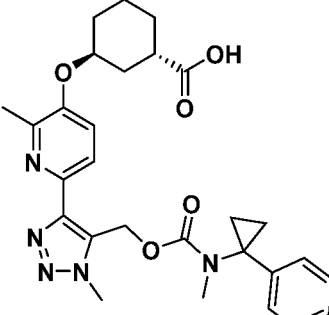
Example	Structure & Name	Analytical & Biology Data	Method
86	 (1S,3S)-3-(((6-(5-(((Dicyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexanecarboxylic acid	LCMS, $[M+H]^+ = 498.3$ $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 7.79 (d, $J = 8.0$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 5.60 - 5.70 (m, 2H), 4.17 (s, 3H), 2.90 (d, $J = 13.2$ Hz, 3H), 2.60 - 2.80 (m, 3H), 2.49 (s, 3H), 2.40 - 2.55 (m, 3H), 2.05 - 2.15 (m, 1H), 1.60 - 1.80 (m, 4H), 1.20 - 1.40 (m, 2H), 0.90 - 1.10 (m, 2H), 0.45 - 0.65 (m, 2H), 0.30 - 0.40 (m, 2H), 0.10 - 0.30 (m, 2H). hLPA1 $\text{IC}_{50} = 54$ nM.	Example 1
87	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 486.0$ $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 7.77 - 7.86 (m, 1 H) 7.44 (d, $J = 8.4$ Hz, 1 H) 5.71 (d, $J = 11.6$ Hz, 2H) 4.81-4.84 (m, 1 H), 4.2 (d, $J = 8.4$ Hz, 1 H), 2.74 - 2.90 (m, 4H), 2.51(s, 3H), 2.10-2.15(m, 1H), 1.91 - 1.97(m, 3H), 1.66-1.74 (m, 4H), 1.28 - 1.37(m, 2H), 1.12 - 1.20 (m, 2H), 0.84 - 0.93 (m, 2H), 0.68 - 0.71(m, 5H), 0.51 - 0.53 (m, 2H). hLPA1 $\text{IC}_{50} = 36$ nM.	Example 1

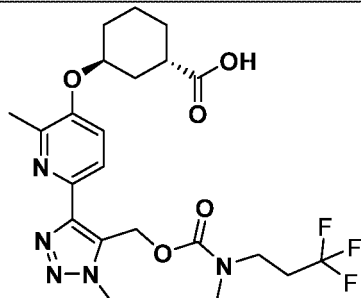
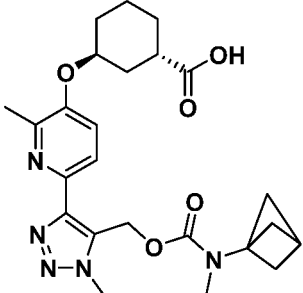
Example	Structure & Name	Analytical & Biology Data	Method
88	 (rac)-trans-3-(((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 490.3$ ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, $J=8.6$ Hz, 1H), 7.24 - 7.17 (m, 1H), 5.71 - 5.62 (m, 2H), 4.71 (tt, $J=6.8, 3.7$ Hz, 1H), 4.58 - 4.13 (m, 1H), 4.07 (s, 3H), 2.65 (br. s., 3H), 2.52 - 2.38 (m, 4H), 2.24 - 1.32 (m, 15H); hLPA1 $\text{IC}_{50} = 32$ nM.	Example 11
89	 (rac)-trans-3-(((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 476.3$ ^1H NMR (500 MHz, CDCl_3) δ 8.46 (d, $J=2.5$ Hz, 1H), 8.05 (d, $J=8.8$ Hz, 1H), 7.56 (dd, $J=8.9, 2.6$ Hz, 1H), 5.50 (s, 2H), 4.89 - 4.75 (m, 1H), 4.55 - 4.44 (m, 1H), 4.10 (s, 3H), 2.64 (br. s., 3H), 2.56 - 2.37 (m, 4H), 2.19 - 1.37 (m, 15H) hLPA1 $\text{IC}_{50} = 32$ nM.	Example 11
90	 (rac)-trans-3-(((6-(5-(((cyclobutyl(methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)-1-fluorocyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 476.3$ ^1H NMR (500 MHz, CDCl_3) δ 8.60 (d, $J=2.5$ Hz, 1H), 8.18 (d, $J=8.5$ Hz, 1H), 7.76 (d, $J=8.8$ Hz, 1H), 5.56 (s, 2H), 4.92 (br. s., 1H), 4.65 - 4.50 (m, 1H), 4.21 (d, $J=3.0$ Hz, 3H), 2.85 (d, $J=17.1$ Hz, 3H), 2.66 - 2.41 (m, 4H), 2.29 - 1.48 (m, 15H) hLPA1 $\text{IC}_{50} = 14$ nM.	Example 11

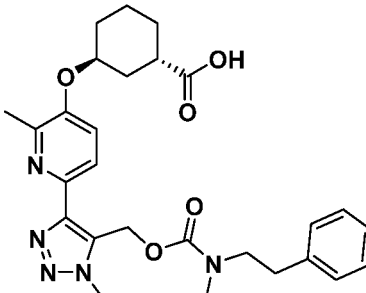
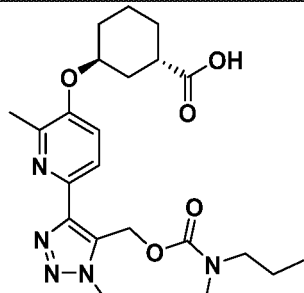
Example	Structure & Name	Analytical & Biology Data	Method
91	 (rac)-trans-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 473.4$ ^1H NMR (500 MHz, CDCl_3) δ 8.11 (d, $J=8.8$ Hz, 1H), 7.80 (t, $J=8.9$ Hz, 1H), 5.70 - 5.42 (m, 2H), 4.86 (br. s., 1H), 4.20 (d, $J=1.7$ Hz, 3H), 3.39 - 3.26 (m, 3H), 2.90 (d, $J=7.7$ Hz, 3H), 2.77 - 2.69 (m, 3H), 2.19 - 1.63 (m, 15H) hLPA1 $\text{IC}_{50} = 18$ nM.	Example 2
92	 (rac)-cis-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.3$ ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, $J=8.6$ Hz, 1H), 7.66 (t, $J=8.6$ Hz, 1H), 5.72 (d, $J=14.5$ Hz, 1H), 5.47 (d, $J=14.3$ Hz, 1H), 4.58 (br. s., 1H), 4.21 (s, 3H), 3.40 - 3.19 (m, 2H), 2.90 (s, 3H), 2.70 (d, $J=2.6$ Hz, 3H), 2.64 - 2.46 (m, 2H), 2.31 - 1.48 (m, 14H) hLPA1 $\text{IC}_{50} = 76$ nM.	Example 2
93	 (1S,3S)-3-(((6-(5-(((cyclobutylmethyl)(methyl-d3)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 475.1$ ^1H NMR (500 MHz, CDCl_3) δ 8.10 (br. s., 1H), 7.87 (br. s., 1H), 5.90 - 5.21 (m, 2H), 4.21 (br. s., 3H), 3.30 (t, $J=8.0$ Hz, 2H), 2.85 (br. s., 1H), 2.73 (br. s., 3H), 2.63 - 2.47 (m, 1H), 2.24 - 1.52 (m, 16H) hLPA1 $\text{IC}_{50} = 20$ nM.	Example 4

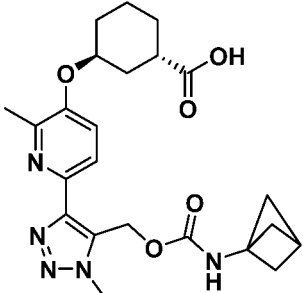
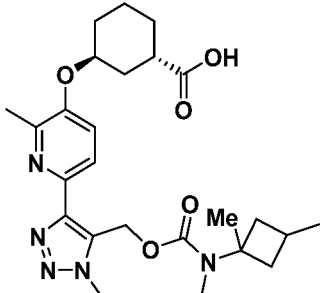
Example	Structure & Name	Analytical & Biology Data	Method
94	 (1S,3S)-3-(4-(5-(1-((cyclopentyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)phenoxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 471.3$ 1H NMR (500 MHz, DMSO-d_6) δ 7.58 (br. S., 2H), 7.05 (d, $J=8.0$ Hz, 2H), 6.00 (d, $J=6.9$ Hz, 1H), 4.69 (br. S., 1H), 4.40 – 4.22 (m, 1H), 4.13 (s, 3H), 2.65 (br. S., 4H), 1.98 – 1.35 (m, 19H) hLPA1 $IC_{50} = 241$ nM.	Example 14
95	 (Cis)-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid; Enantiomer A	LCMS, $[M+H]^+ = 472.3$ 1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, $J=8.1$ Hz, 1H), 7.16 (dd, $J=8.3$, 3.6 Hz, 1H), 5.74 (br. S., 2H), 4.32 – 4.18 (m, 1H), 4.13 (br. S., 3H), 3.35 – 3.11 (m, 2H), 2.92 – 2.75 (m, 3H), 2.56 – 2.24 (m, 5H), 2.17 – 1.35 (m, 15H) hLPA1 $IC_{50} = 1152$ nM.	Example 1
96	 (Cis)-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid Enantiomer B	LCMS, $[M+H]^+ = 472.3$ 1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, $J=8.6$ Hz, 1H), 7.11 (d, $J=8.6$ Hz, 1H), 5.67 (br. s., 2H), 4.23 – 4.12 (m, 1H), 4.06 (br. s., 3H), 3.31 – 3.01 (m, 2H), 2.86 – 2.65 (m, 3H), 2.42 – 2.30 (m, 4H), 2.16 – 1.31 (m, 15H) hLPA1 $IC_{50} = 20$ nM.	Example 1

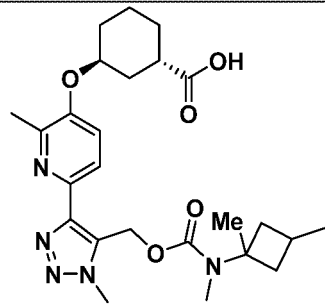
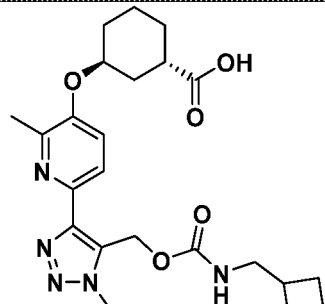
Example	Structure & Name	Analytical & Biology Data	Method
97	 (1R,3R)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.3$ 1H NMR (400 MHz, $CDCl_3$) δ 8.03 - 7.90 (m, 1H), 7.23 (d, $J=8.6$ Hz, 1H), 5.77 (br d, $J=5.3$ Hz, 2H), 4.72 (br s, 1H), 4.16 (br s, 3H), 3.38 - 3.15 (m, 2H), 2.90 (br s, 3H), 2.80 (br s, 2H), 2.59 (br s, 1H), 2.45 - 2.36 (m, 1H), 2.23 - 2.10 (m, 1H), 2.08 - 1.52 (m, 14H) hLPA1 $IC_{50} = 10$ nM.	Example 1
98	 (1S,3S)-3-((6-(5-(((2-fluorobenzyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 512.3$ 1H NMR (600 MHz, $DMSO-d_6$) δ 7.84 (d, $J=5.2$ Hz, 1H), 7.46 (br s., 1H), 7.41 - 6.79 (m, 4H), 5.87 - 5.59 (m, 2H), 4.78 (br s., 1H), 4.51 - 4.26 (m, 2H), 4.15 - 3.91 (m, 3H), 3.53 - 3.37 (m, 1H), 2.87 - 2.69 (m, 3H), 2.67 - 2.58 (m, 1H), 2.46 - 2.30 (m, 3H), 2.07 - 1.44 (m, 8H) hLPA1 $IC_{50} = 19$ nM.	Example 1

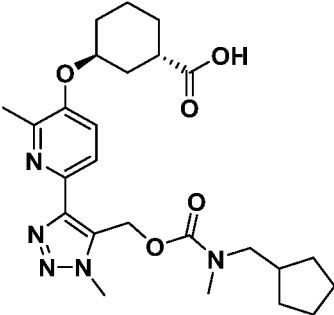
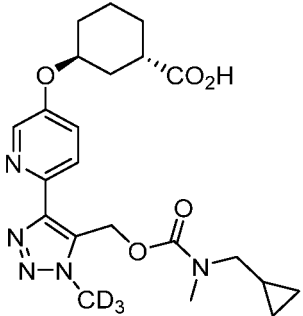
Example	Structure & Name	Analytical & Biology Data	Method
99	 (1S,3S)-3-(((6-(5-(((1-cyclobutylpropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (diastereomeric mixture)	LCMS, $[M+H]^+ = 486.3$ 1H NMR (600 MHz, DMSO-d_6) δ 7.47 (d, $J=8.5$ Hz, 1H), 6.98 (d, $J=9.1$ Hz, 1H), 5.65 (br. s., 2H), 4.77 (br. s., 1H), 4.07 (s, 3H), 3.51 (br. s., 4H), 2.66 - 2.57 (m, 1H), 2.40 (br. s., 3H), 2.29 - 2.19 (m, 1H), 2.05 - 1.97 (m, 1H), 1.89 - 1.43 (m, 14H), 1.25 (d, $J=7.3$ Hz, 3H), 0.76 (t, $J=7.3$ Hz, 3H) hLPA1 $IC_{50} = 144$ nM.	Example 1
100	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-phenylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 520.0$ 1H NMR (400 MHz, CD_3OD) δ 7.60 - 7.69 (m, 1 H) 7.01 - 7.34 (m, 5 H) 6.78 - 6.88 (m, 1 H) 5.60 - 5.68 (m, 2 H) 4.08 - 4.14 (m, 1 H) 3.76 - 3.86 (m, 3 H) 2.88 - 2.94 (m, 3 H) 2.80 - 2.83 (m, 1 H) 2.32 - 2.44 (m, 3H) 1.86 - 1.92 (m, 4 H) 1.54 - 1.67 (m, 4 H) 1.18 - 1.27 (m, 4 H) hLPA1 $IC_{50} = 70$ nM.	Example 5

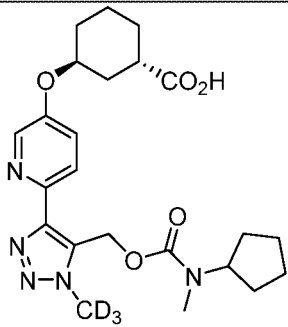
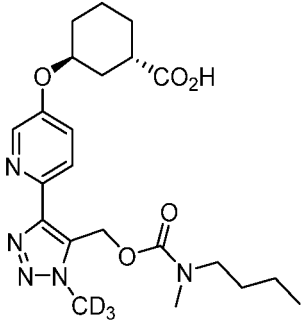
Example	Structure & Name	Analytical & Biology Data	Method
101	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(3,3,3-trifluoropropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 500.0$ 1H NMR (400 MHz, CD_3OD) δ 7.60 - 7.69 (m, 1 H) 7.01 - 7.34 (m, 5 H) 6.78 - 6.88 (m, 1 H) 5.60 - 5.68 (m, 2 H) 4.08 - 4.14 (m, 1 H) 3.76 - 3.86 (m, 3 H) 2.88 - 2.94 (m, 3 H) 2.80 - 2.83 (m, 1 H) 2.32 - 2.44 (m, 3H) 1.86 - 1.92 (m, 4 H) 1.54 - 1.67 (m, 4 H) 1.18 - 1.27 (m, 4 H) hLPA1 $IC_{50} = 49$ nM.	Example 5
102	 (1S,3S)-3-((6-(5-(((bicyclo[1.1.1]pentan-1-yl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 469.9$ 1H NMR (500 MHz, $DMSO-d_6$) δ 7.83 (d, $J=8.4$ Hz, 1H), 7.48 (d, $J=8.6$ Hz, 1H), 5.61 (s, 2H), 4.87 - 4.69 (m, 1H), 4.10 (s, 3H), 2.71 (br. s., 3H), 2.55 (s, 3H), 2.40 (s, 3H), 2.07 - 1.47 (m, 15H) hLPA1 $IC_{50} = 53$ nM.	Example 1

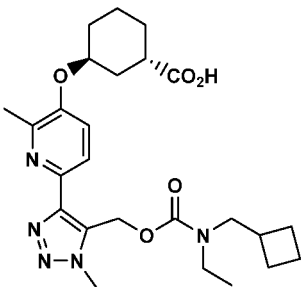
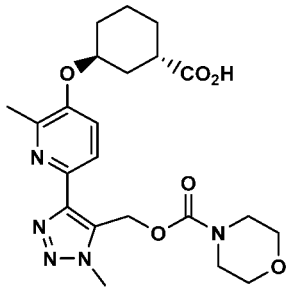
Example	Structure & Name	Analytical & Biology Data	Method
103	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(phenethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 508.2$ 1H NMR (400 MHz, CD_3OD) δ 7.84 - 7.88 (m, 1 H) 7.46 (br. s., 1 H) 7.12 - 7.31 (m, 4 H) 6.97 - 7.01 (m, 1 H) 5.60 - 5.73 (m, 2H) 4.80 (br. s., 1 H) 4.12 (br. s., 3 H) 3.46 - 3.53 (m, 3 H) 2.74 - 2.85 (m, 4 H) 2.63 (d, $J=7.03$ Hz, 1 H) 2.46 (br. s., 3 H) 2.09 (br. s., 1 H) 1.94 (br. s., 3 H) 1.61 - 1.73 (m, 4 H) hLPA1 $IC_{50} = 119$ nM.	Example 5
104	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 446.1$ 1H NMR (400 MHz, CD_3OD) δ 7.81 (d, $J=8.53$ Hz, 1 H) 7.44 (d, $J=8.53$ Hz, 1 H) 5.71 (br. s., 2 H) 4.81 (br. s., 1 H) 4.19 (s, 3 H) 3.09 - 3.17 (m, 2 H) 2.81 - 2.90 (m, 4 H) 2.51 (s, 3 H) 2.14 (br. s., 1 H) 1.88 - 1.92 (m, 3 H) 1.68 - 1.71 (m, 4 H) 1.56 (br. s., 2 H) 0.88 (d, $J=7.03$ Hz, 3 H) hLPA1 $IC_{50} = 19$ nM	Example 5

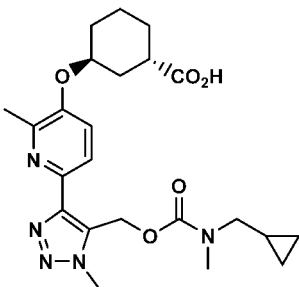
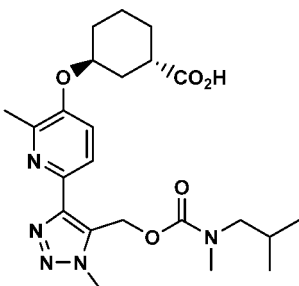
Example	Structure & Name	Analytical & Biology Data	Method
105	 (1S,3S)-3-(((6-(5-(((bicyclo[1.1.1]pentan-1-ylcarbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 456.3$ hLPA1 IC₅₀ = 576 nM.	Example 3
106	 (1S,3S)-3-(((6-(5-(((1,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid Enantiomer A	LCMS, $[M+H]^+ = 486.1$ ¹H NMR (400 MHz, CD₃OD) δ 7.79 (d, <i>J</i>=8.53 Hz, 1 H) 7.44 (d, <i>J</i>=8.53 Hz, 1 H) 5.66 (s, 2 H) 4.19 (s, 3H) 2.68 (d, <i>J</i>=6.02 Hz, 1 H) 2.52 (s, 3 H) 2.12 (d, <i>J</i>=13.05 Hz, 3 H) 1.94 (br. s., 3H) 1.58 - 1.79 (m, 5H) 1.31 (br. s., 6 H) 1.13 (br. s., 3 H) 0.93 - 0.96 (m, 3 H) hLPA1 IC₅₀ = 67 nM.	Example 5

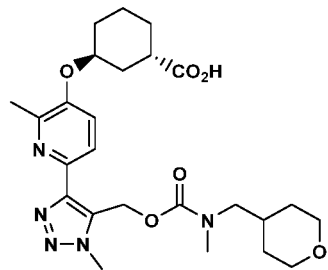
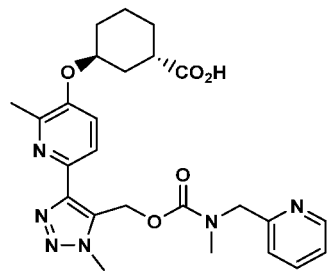
Example	Structure & Name	Analytical & Biology Data	Method
107	 (1S,3S)-3-(((6-(5-(((1,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid Enantiomer B	LCMS, $[M+H]^+ = 486.1$ 1H NMR (400 MHz, CD_3OD) δ ppm 7.79 (d, $J=8.53$ Hz, 1 H) 7.44 (d, $J=8.53$ Hz, 1 H) 5.66 (s, 2 H) 4.19 (s, 3H) 2.68 (d, $J=6.02$ Hz, 1 H) 2.52 (s, 3 H) 2.12 (d, $J=13.05$ Hz, 3 H) 1.94 (br. s., 3H) 1.58 - 1.79 (m, 5H) 1.31 (br. s., 6 H) 1.13 (br. s., 3 H) 0.93 - 0.96 (m, 3 H) hLPA1 $IC_{50} = 70$ nM.	Example 5
108	 (1S,3S)-3-(((6-(5-(((cyclobutyl)methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 458.0$ 1H NMR (500 MHz, $DMSO-d_6$) δ 7.83 (d, $J=8.2$ Hz, 1H), 7.58 - 7.37 (m, 1H), 7.29 (br. s., 1H), 5.64 (s, 2H), 4.77 (br. s., 1H), 4.07 (s, 3H), 3.01 (t, $J=6.0$ Hz, 2H), 2.44 - 2.31 (m, 4H), 2.05 - 1.40 (m, 15H) hLPA1 $IC_{50} = 108$ nM.	Example 1

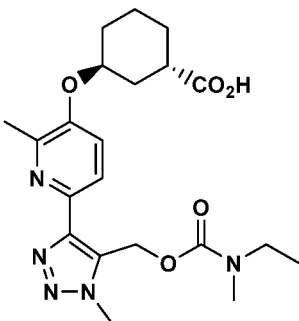
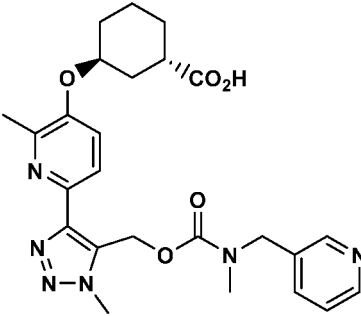
Example	Structure & Name	Analytical & Biology Data	Method
109	 (1S,3S)-3-(((6-(5-((((cyclopentylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 486.2$ 1H NMR (400 MHz, DMSO-d_6) δ 6.97 - 7.04 (m, 1 H) 6.60 - 6.67 (m, 1 H) 4.89 (s, 2 H) 3.99 - 4.01 (m, 1 H) 3.38 (s, 3 H) 2.39 - 2.43 (m, 1 H) 2.26 - 2.30 (m, 1 H) 2.08 (s, 3 H) 1.70 (s, 3 H) 1.28 - 1.33 (m, 1 H) 1.10 - 1.19 (m, 4 H) 0.46 - 0.98 (m, 12 H) 0.39 - 0.42 (m, 1 H) hLPA1 $IC_{50} = 22$ nM.	Example 5
110	 (1S,3S)-3-(((6-(5-((((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-(methyl-d_3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 447.4$ 1H NMR (500 MHz, DMSO-d_6) δ 8.34 (br. s., 1H), 7.98 (d, $J=7.7$ Hz, 1H), 7.53 (d, $J=7.5$ Hz, 1H), 7.36 - 6.86 (m, 1H), 6.03 - 5.43 (m, 2H), 4.77 (br. s., 1H), 3.26 - 2.57 (m, 6H), 2.19 - 1.31 (m, 8H), 1.07 - 0.65 (m, 1H), 0.62 - -0.21 (m, 4H) hLPA1 $IC_{50} = 31$ nM.	Example 4

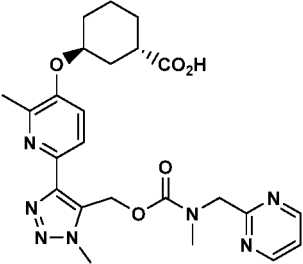
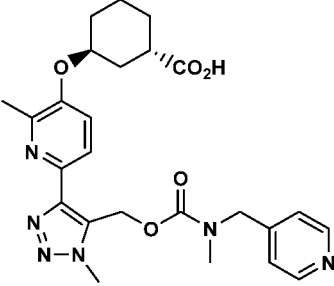
Example	Structure & Name	Analytical & Biology Data	Method
111	 (1S,3S)-3-(((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-(methyl-d3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 461.2$ 1H NMR (500 MHz, DMSO-d_6) δ 8.33 (d, $J=2.4$ Hz, 1H), 7.98 (d, $J=8.8$ Hz, 1H), 7.53 (d, $J=6.3$ Hz, 1H), 5.60 (br. s., 2H), 4.77 (br. s., 1H), 3.59 (br. s., 1H), 2.63 (br. s., 4H), 1.94 (br. s., 1H), 1.86 - 1.69 (m, 3H), 1.68 - 1.25 (m, 12H) hLPA1 $IC_{50} = 23$ nM.	Example 4
112	 (1S,3S)-3-(((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-(methyl-d3)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 449.4$ 1H NMR (500 MHz, DMSO-d_6) δ 8.34 (d, $J=2.3$ Hz, 1H), 7.98 (d, $J=8.8$ Hz, 1H), 7.54 (d, $J=7.6$ Hz, 1H), 5.83 - 5.25 (m, 2H), 4.77 (br. s., 1H), 3.29 - 2.97 (m, 2H), 2.85 - 2.59 (m, 4H), 1.94 (br. s., 1H), 1.88 - 1.71 (m, 3H), 1.68 - 1.33 (m, 5H), 1.31 - 1.14 (m, 2H), 1.08 - 0.55 (m, 4H) hLPA1 $IC_{50} = 17$ nM.	Example 4

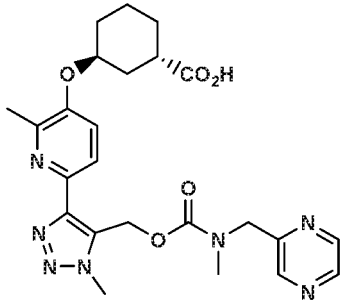
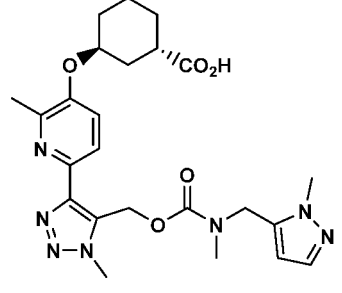
Example	Structure & Name	Analytical & Biology Data	Method
113	 (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(ethyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 486.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.99 - 7.72 (m, 1H), 7.48 (br d, $J=7.4$ Hz, 1H), 5.62 (br s, 3H), 4.79 (br s, 1H), 4.10 (br s, 4H), 3.31 - 2.96 (m, 5H), 2.71 - 2.59 (m, 1H), 2.41 (br s, 3H), 1.97 - 1.77 (m, 6H), 1.59 - 1.34 (m, 6H), 1.07 - 0.76 (m, 4H) hLPA_I IC₅₀ = 15 nM	Example 1
114	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((morpholine-4-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 460.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.80 (br d, $J=8.6$ Hz, 1H), 7.45 (br d, $J=8.7$ Hz, 1H), 5.65 (s, 2H), 4.76 (br s, 1H), 4.06 (s, 2H), 3.93 - 3.84 (m, 2H), 3.61 - 3.17 (m, 7H), 2.66 - 2.58 (m, 1H), 2.39 (s, 3H), 2.12 - 1.29 (m, 8H) hLPA_I IC₅₀ = 643 nM	Example 1

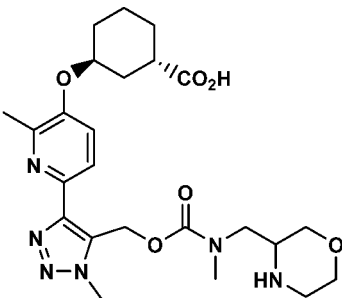
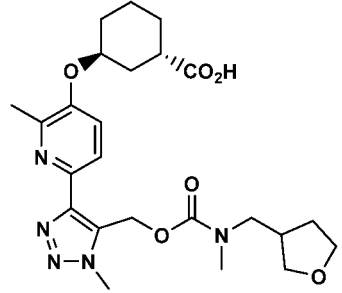
Example	Structure & Name	Analytical & Biology Data	Method
115	 (1S,3S)-3-((6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 458.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.2$ Hz, 1H), 7.48 (br d, $J=7.7$ Hz, 1H), 5.86 - 5.45 (m, 2H), 4.78 (br s, 1H), 4.10 (s, 3H), 3.12 - 2.92 (m, 2H), 2.89 - 2.76 (m, 3H), 2.62 (br s, 1H), 2.41 (s, 3H), 2.09 - 1.42 (m, 8H), 0.97 - 0.64 (m, 1H), 0.55 - -0.10 (m, 4H) hLPA₁ IC₅₀ = 18 nM	Example 1
116	 (1S,3S)-3-((6-(5-((isobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 460.2$ 1H NMR (500 MHz, DMSO-d_6) δ 8.03 - 7.74 (m, 1H), 7.47 (br d, $J=7.7$ Hz, 1H), 6.06 - 5.43 (m, 2H), 4.78 (br s, 1H), 4.10 (s, 3H), 3.02 (br d, $J=6.8$ Hz, 1H), 2.88 (br d, $J=6.9$ Hz, 1H), 2.81 - 2.69 (m, 3H), 2.62 (br t, $J=10.2$ Hz, 1H), 2.41 (s, 3H), 2.12 - 1.42 (m, 9H), 0.81 (br d, $J=6.1$ Hz, 3H), 0.62 (br d, $J=5.8$ Hz, 3H) hLPA₁ IC₅₀ = 29 nM	Example 1

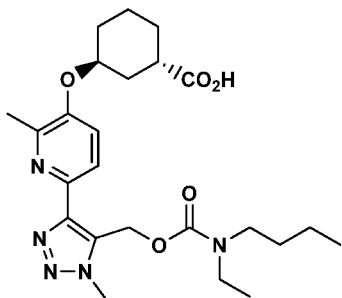
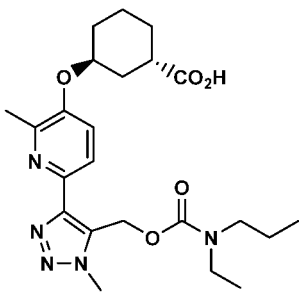
Example	Structure & Name	Analytical & Biology Data	Method
117	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((tetrahydro-2H-pyran-4-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 502.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.85 (br d, $J=6.1$ Hz, 1H), 7.48 (br d, $J=8.6$ Hz, 1H), 5.73 - 5.48 (m, 2H), 4.78 (br s, 1H), 4.10 (br d, $J=7.7$ Hz, 3H), 3.82 (br d, $J=8.8$ Hz, 1H), 3.62 (br d, $J=12.5$ Hz, 1H), 3.24 (br s, 1H), 3.17 (s, 1H), 3.09 (br d, $J=6.3$ Hz, 1H), 3.04 - 2.92 (m, 2H), 2.84 - 2.72 (m, 3H), 2.41 (s, 3H), 2.05 - 1.10 (m, 13H) hLPA1 $IC_{50} = 17$ nM	Example 1
118	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyridin-2-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 495.0$ 1H NMR (500 MHz, DMSO-d_6) δ 8.69 - 7.72 (m, 2H), 7.72 - 7.03 (m, 4H), 5.79 - 5.58 (m, 2H), 4.78 (br s, 1H), 4.45 (s, 2H), 4.27 - 3.82 (m, 2H), 3.17 (s, 1H), 2.97 - 2.75 (m, 3H), 2.63 (br s, 1H), 2.44 - 2.29 (m, 3H), 2.02 (br d, $J=12.7$ Hz, 1H), 1.93 - 1.40 (m, 7H) hLPA1 $IC_{50} = 211$ nM	Example 1

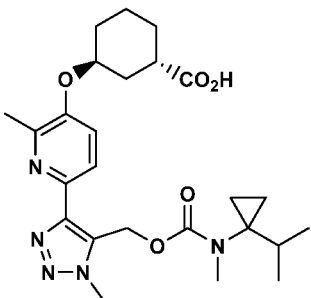
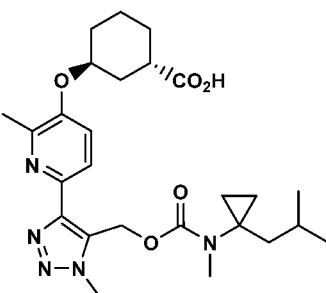
Example	Structure & Name	Analytical & Biology Data	Method
119	 (1S,3S)-3-((6-(5-(((ethyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 432.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.48 (br d, $J=8.6$ Hz, 1H), 5.64 (br d, $J=13.1$ Hz, 2H), 4.78 (br s, 1H), 4.09 (s, 3H), 3.31 - 3.04 (m, 2H), 2.84 - 2.70 (m, 3H), 2.62 (br s, 1H), 2.41 (s, 3H), 2.01 (br d, $J=14.1$ Hz, 1H), 1.92 - 1.72 (m, 3H), 1.69 - 1.43 (m, 4H), 1.08 - 0.78 (m, 3H) hLPA₁ IC₅₀ = 878 nM	Example 1
120	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyridin-3-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 495.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.64 - 8.27 (m, 2H), 7.85 (d, $J=8.6$ Hz, 1H), 7.70 - 7.31 (m, 2H), 6.59 (s, 1H), 5.81 - 5.57 (m, 2H), 4.79 (br s, 1H), 4.52 - 4.27 (m, 2H), 4.20 - 3.96 (m, 2H), 3.39 (br s, 1H), 2.98 - 2.70 (m, 3H), 2.63 (br d, $J=9.8$ Hz, 1H), 2.38 (br d, $J=17.8$ Hz, 2H), 2.10 - 1.96 (m, 1H), 1.91 - 1.04 (m, 8H) hLPA₁ IC₅₀ = 809 nM	Example 1

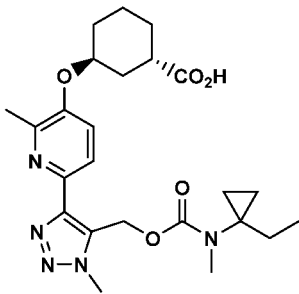
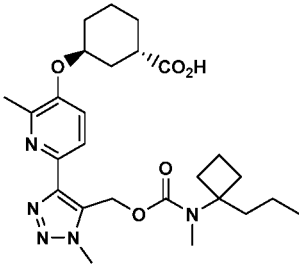
Example	Structure & Name	Analytical & Biology Data	Method
121	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyrimidin-2-ylmethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 496.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.76 (br d, $J=4.9$ Hz, 1H), 8.61 (d, $J=4.9$ Hz, 1H), 7.95 - 7.68 (m, 1H), 7.50 - 7.20 (m, 2H), 5.85 - 5.44 (m, 2H), 4.77 (br s, 1H), 4.67 - 4.49 (m, 2H), 4.13 (s, 1H), 2.95 - 2.75 (m, 4H), 2.64 (br s, 1H), 2.44 - 2.33 (m, 4H), 2.09 - 1.97 (m, 1H), 1.91 - 1.74 (m, 4H), 1.68 - 1.48 (m, 4H) hLPA1 $\text{IC}_{50} = 1087$ nM	Example 1
122	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyridin-4-ylmethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 495.0$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.85 - 8.33 (m, 1H), 8.06 - 7.72 (m, 1H), 7.58 - 7.39 (m, 2H), 7.37 - 6.99 (m, 2H), 6.04 - 5.53 (m, 2H), 4.87 - 4.31 (m, 2H), 4.23 - 3.84 (m, 3H), 3.17 (s, 1H), 2.93 - 2.73 (m, 3H), 2.67 - 2.57 (m, 1H), 2.43 - 2.29 (m, 3H), 2.02 (br d, $J=13.9$ Hz, 1H), 1.90 - 1.73 (m, 2H), 1.66 - 1.47 (m, 2H), 1.37 - 1.14 (m, 2H), 1.00 (br d, $J=6.1$ Hz, 1H), 0.85 (br d, $J=6.3$ Hz, 1H) hLPA1 $\text{IC}_{50} = 873$ nM	Example 1

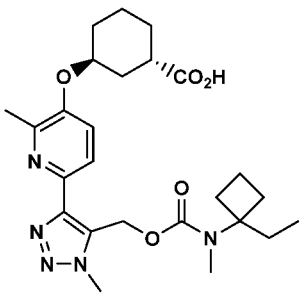
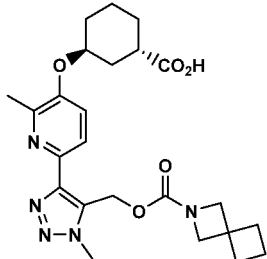
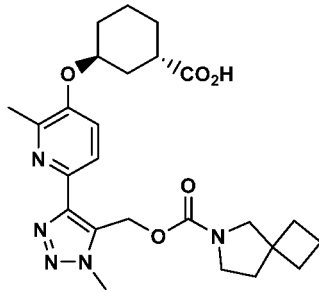
Example	Structure & Name	Analytical & Biology Data	Method
123	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(pyrazin-2-ylmethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 496.1$ 1H NMR (500 MHz, DMSO-d_6) δ 8.63 - 8.51 (m, 1H), 8.47 - 8.30 (m, 1H), 7.96 - 7.59 (m, 1H), 7.56 - 7.27 (m, 1H), 6.05 - 5.37 (m, 2H), 4.77 (br s, 1H), 4.62 - 4.39 (m, 2H), 4.24 - 3.84 (m, 3H), 3.45 (br s, 1H), 2.98 - 2.76 (m, 3H), 2.63 (br s, 1H), 2.41 - 2.24 (m, 3H), 2.15 - 1.35 (m, 8H) hLPA1 $IC_{50} = 618$ nM	Example 1
124	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((1-methyl-1H-pyrazol-5-yl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 498.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.5$ Hz, 1H), 7.49 (d, $J=8.5$ Hz, 1H), 7.41 - 7.12 (m, 1H), 6.14 (br s, 1H), 5.70 (br s, 2H), 5.13 - 3.29 (m, 7H), 2.71 (br s, 3H), 2.59 - 2.55 (m, 2H), 2.39 (s, 3H), 2.14 - 1.31 (m, 9H) hLPA1 $IC_{50} = 982$ nM	Example 1

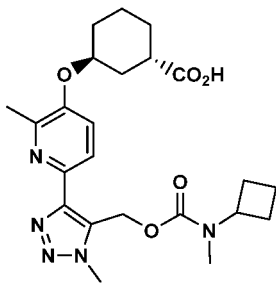
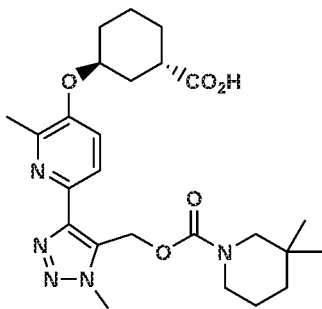
Example	Structure & Name	Analytical & Biology Data	Method
125	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(morpholin-3-ylmethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 504.0$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 2H), 7.49 (br d, $J=8.5$ Hz, 1H), 6.00 - 5.25 (m, 3H), 4.75 (br s, 2H), 4.10 (br s, 4H), 2.90 - 2.72 (m, 3H), 2.41 (s, 4H), 2.14 - 1.31 (m, 13H) hLPA1 $IC_{50} = 668$ nM	Example 1
126	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(tetrahydrofuran-3-ylmethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 488.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.94 (br d, $J=8.9$ Hz, 1H), 7.83 (d, $J=8.5$ Hz, 1H), 7.48 (br d, $J=8.5$ Hz, 1H), 6.52 (br d, $J=8.2$ Hz, 1H), 5.65 (br s, 2H), 4.76 (br s, 1H), 4.09 (s, 3H), 3.55 - 2.96 (m, 3H), 2.85 - 2.70 (m, 3H), 2.60 - 2.56 (m, 1H), 2.40 (s, 3H), 2.33 - 2.23 (m, 1H), 2.03 - 1.19 (m, 11H) hLPA1 $IC_{50} = 346$ nM	Example 1

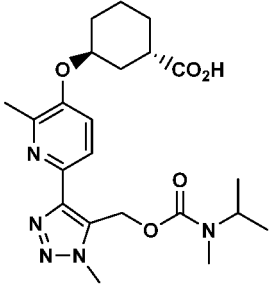
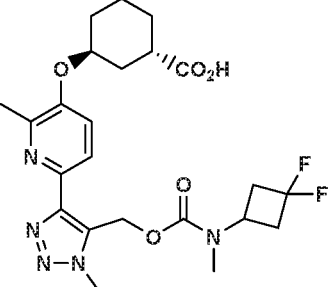
Example	Structure & Name	Analytical & Biology Data	Method
127	 (1S,3S)-3-(((6-(5-(((butyl(ethyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 474.2$ 1H NMR (500 MHz, DMSO-d_6) δ 7.81 (br d, $J=8.5$ Hz, 1H), 7.44 (br d, $J=8.5$ Hz, 1H), 5.58 (s, 2H), 4.75 (br s, 1H), 4.08 (s, 3H), 3.23 - 2.91 (m, 4H), 2.60 (br s, 1H), 2.39 (s, 3H), 2.05 - 1.93 (m, 1H), 1.89 - 1.71 (m, 3H), 1.66 - 1.37 (m, 4H), 1.25 - 1.12 (m, 4H), 1.06 - 0.77 (m, 5H), 0.58 (br s, 2H) hLPA1 $IC_{50} = 33$ nM	Example 1
128	 (1S,3S)-3-(((6-(5-(((ethyl(propyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC/MS: $[M+H]^+ = 460.3$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.47 (d, $J=8.5$ Hz, 1H), 5.61 (s, 2H), 4.78 (br s, 1H), 4.09 (s, 3H), 3.42 - 3.33 (m, 1H), 3.23 - 2.96 (m, 4H), 2.62 (br t, $J=10.4$ Hz, 1H), 2.41 (s, 3H), 2.01 (br d, $J=13.7$ Hz, 1H), 1.91 - 1.73 (m, 3H), 1.68 - 1.41 (m, 5H), 1.28 (br s, 1H), 1.00 (br d, $J=6.1$ Hz, 1H), 0.92 - 0.76 (m, 3H), 0.62 (br s, 1H) hLPA1 $IC_{50} = 158$ nM	Example 3

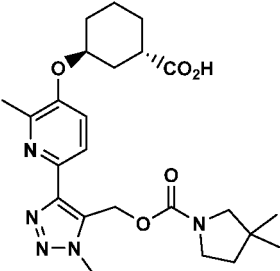
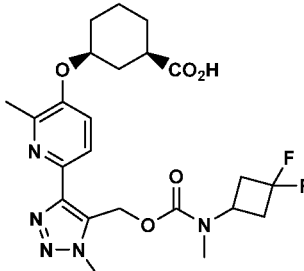
Example	Structure & Name	Analytical & Biology Data	Method
129	 (1S,3S)-3-(((6-(5-(((1-isopropylcyclopropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 486$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.81 (br d, $J=8.2$ Hz, 1H), 7.46 (br d, $J=8.5$ Hz, 1H), 5.60 (br s, 2H), 4.78 (br s, 1H), 4.15 - 4.03 (m, 3H), 3.53 (br s, 1H), 2.80 - 2.70 (m, 3H), 2.65 - 2.57 (m, 1H), 2.41 (s, 3H), 2.05 - 1.96 (m, 1H), 1.89 - 1.72 (m, 3H), 1.66 - 1.46 (m, 4H), 0.86 - 0.82 (m, 2H), 0.76 - 0.48 (m, 8H) hLPA1 $\text{IC}_{50} = 352$ nM	Example 3
130	 (1S,3S)-3-(((6-(5-(((1-isobutylcyclopropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 500$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.82 (br d, $J=8.5$ Hz, 1H), 7.46 (br d, $J=8.5$ Hz, 1H), 5.59 (br s, 2H), 4.77 (br s, 1H), 4.15 - 4.02 (m, 3H), 3.59 (br s, 1H), 2.79 - 2.66 (m, 3H), 2.63 - 2.56 (m, 1H), 2.39 (s, 3H), 2.04 - 1.94 (m, 1H), 1.88 - 1.71 (m, 3H), 1.66 - 1.44 (m, 4H), 1.15 - 1.08 (m, 1H), 0.90 - 0.85 (m, 2H), 0.83 - 0.32 (m, 9H) hLPA1 $\text{IC}_{50} = 243$ nM	Example 10

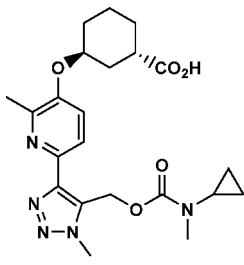
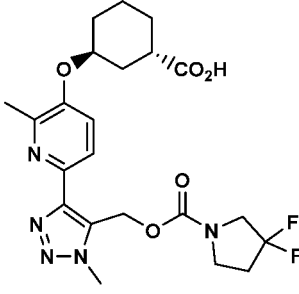
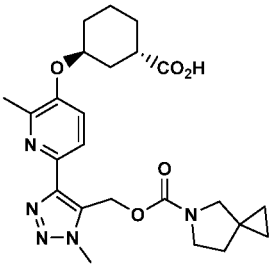
Example	Structure & Name	Analytical & Biology Data	Method
131	 (1S,3S)-3-((6-(5-(((1-ethylcyclopropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.80 (br d, $J=7.9$ Hz, 1H), 7.46 (br d, $J=8.2$ Hz, 1H), 5.60 (s, 2H), 4.81 - 4.71 (m, 1H), 4.15 - 4.01 (m, 3H), 3.66 (br s, 3H), 2.78 - 2.66 (m, 3H), 2.61 - 2.55 (m, 1H), 2.40 (s, 3H), 2.02 - 1.93 (m, 1H), 1.85 - 1.73 (m, 3H), 1.64 - 1.44 (m, 5H), 0.85 - 0.76 (m, 1H), 0.67 - 0.57 (m, 4H), 0.44 (br s, 1H) hLPA1 $\text{IC}_{50} = 187$ nM	Example 10
132	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(1-propylcyclobutyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 500$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.01 - 7.78 (m, 1H), 7.49 (br d, $J=4.6$ Hz, 1H), 5.58 (br s, 2H), 4.78 (br s, 1H), 4.09 (br s, 3H), 3.54 - 3.32 (m, 2H), 2.63 - 2.58 (m, 3H), 2.46 - 2.32 (m, 3H), 2.08 - 1.97 (m, 3H), 1.91 - 1.74 (m, 4H), 1.70 - 1.47 (m, 8H), 1.28 - 1.19 (m, 1H), 1.07 - 0.79 (m, 3H), 0.62 - 0.56 (m, 1H) hLPA1 $\text{IC}_{50} = 180$ nM	Example 10

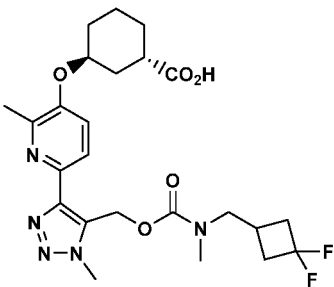
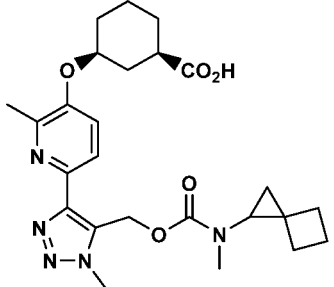
Example	Structure & Name	Analytical & Biology Data	Method
133	 (1S,3S)-3-(((6-(5-((((1-ethylcyclobutyl)(methyl)carbamoyloxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 486$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.81 (br d, $J=7.3$ Hz, 1H), 7.48 (br d, $J=8.5$ Hz, 1H), 5.57 (br s, 2H), 4.82 - 4.73 (m, 1H), 4.08 (s, 3H), 2.64 - 2.57 (m, 3H), 2.41 (s, 3H), 2.23 - 1.74 (m, 9H), 1.70 - 1.44 (m, 8H), 0.92 - 0.41 (m, 3H) hLPA1 $\text{IC}_{50} = 174$ nM	Example 10
134	 (1S,3S)-3-(((6-(5-(((2-azaspiro[3.3]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 470$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.9$ Hz, 1H), 5.62 (s, 2H), 4.77 (br s, 1H), 4.06 (s, 3H), 3.90 (s, 1H), 3.81 (br s, 3H), 2.64 - 2.58 (m, 1H), 2.41 (s, 3H), 2.10 - 1.97 (m, 5H), 1.88 - 1.75 (m, 3H), 1.74 - 1.50 (m, 6H) hLPA1 $\text{IC}_{50} = 76$ nM	Example 1
135	 (1S,3S)-3-(((6-(5-(((6-azaspiro[3.4]octane-6-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.79 (br d, $J=8.2$ Hz, 1H), 7.44 (br d, $J=8.5$ Hz, 1H), 5.62 - 5.56 (m, 2H), 4.74 (br s, 1H), 4.08 - 4.04 (m, 2H), 3.86 - 3.61 (m, 2H), 3.18 (s, 3H), 3.04 (s, 1H), 2.62 - 2.56 (m, 1H), 2.38 (s, 3H), 2.01 - 1.92 (m, 1H), 1.90 - 1.71 (m, 10H), 1.65 - 1.41 (m, 4H) hLPA1 $\text{IC}_{50} = 47$ nM	Example 1

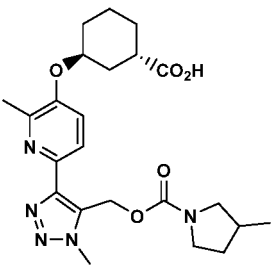
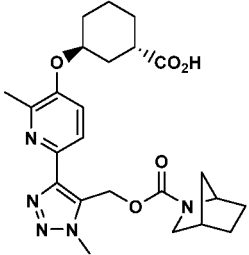
Example	Structure & Name	Analytical & Biology Data	Method
136	 (1S,3S)-3-(((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 458$ ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, $J=8.5$ Hz, 1H), 7.25 (d, $J=8.8$ Hz, 1H), 5.77 (s, 2H), 4.76 - 4.71 (m, 1H), 4.17 - 4.13 (m, 4H), 2.93 - 2.82 (m, 3H), 2.53 (s, 3H), 2.07 (s, 10H), 1.68 (br s, 5H) hLPA1 $\text{IC}_{50} = 36$ nM	Example 1
137	 (1S,3S)-3-(((6-(5-(((3,3-dimethylpiperidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 586$ ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.47 (br d, $J=8.9$ Hz, 1H), 5.62 (br s, 2H), 4.77 (br s, 1H), 4.09 (s, 3H), 3.30 - 2.86 (m, 4H), 2.61 - 2.57 (m, 1H), 2.41 (s, 3H), 2.03 - 1.92 (m, 1H), 1.88 - 1.72 (m, 3H), 1.62 (br d, $J=9.2$ Hz, 5H), 1.31 - 1.19 (m, 4H), 0.89 - 0.75 (m, 3H), 0.73 - 0.60 (m, 3H) hLPA1 $\text{IC}_{50} = 292$ nM	Example 1

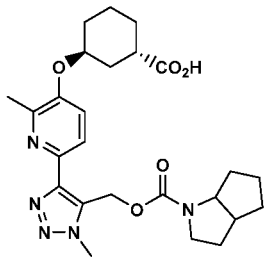
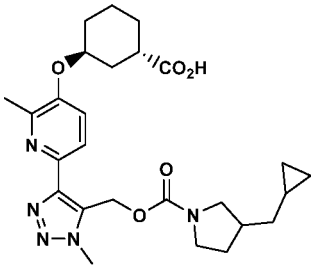
Example	Structure & Name	Analytical & Biology Data	Method
138	 (1S,3S)-3-((6-(5-(((isopropyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 446$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.3$ Hz, 1H), 7.48 (br d, $J=8.6$ Hz, 1H), 5.63 (br s, 2H), 4.79 (br s, 1H), 4.09 (s, 3H), 3.91 - 3.90 (m, 1H), 2.69 - 2.61 (m, 3H), 2.41 (s, 3H), 1.62 (br s, 9H), 1.03 (br s, 3H), 0.93 (br s, 3H) hLPA1 $\text{IC}_{50} = 98$ nM	Example 3
139	 (1S,3S)-3-((6-(5-(((3,3-difluorocyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 494$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, $J=8.2$ Hz, 1H), 7.48 (d, $J=8.9$ Hz, 1H), 5.66 (br s, 2H), 4.78 (br s, 1H), 4.10 (s, 3H), 2.82 - 2.68 (m, 5H), 2.67 - 2.59 (m, 2H), 2.41 (s, 3H), 2.06 - 1.97 (m, 1H), 1.94 - 1.71 (m, 3H), 1.68 - 1.42 (m, 4H), 1.24 (s, 2H) hLPA1 $\text{IC}_{50} = 70$ nM	Example 10

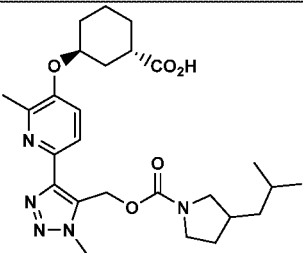
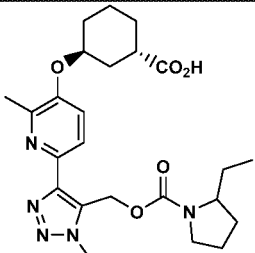
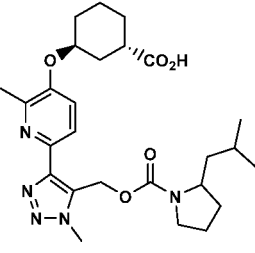
Example	Structure & Name	Analytical & Biology Data	Method
140	 (1S,3S)-3-((6-(5-(((3,3-dimethylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.47 (br d, $J=8.5$ Hz, 1H), 5.65 (br d, $J=4.6$ Hz, 2H), 4.78 (br s, 1H), 4.08 (br d, $J=4.6$ Hz, 3H), 3.36 - 3.21 (m, 1H), 3.02 (s, 1H), 2.90 (s, 1H), 2.62 (br s, 1H), 2.41 (s, 3H), 2.06 - 1.96 (m, 1H), 1.80 (br s, 3H), 1.57 (br t, $J=7.2$ Hz, 6H), 1.23 (s, 2H), 0.99 (s, 3H), 0.94 (s, 3H) hLPA1 $\text{IC}_{50} = 148$ nM	Example 1
141	 (1R,3S)-3-((6-(5-(((3,3-difluorocyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid; cis isomer from epimerization in final ester hydrolysis	LCMS, $[M+H]^+ = 494$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.2$ Hz, 1H), 7.52 (d, $J=8.5$ Hz, 1H), 5.65 (br s, 2H), 4.45 - 4.38 (m, 1H), 4.10 (s, 3H), 2.79 - 2.74 (m, 4H), 2.70 - 2.62 (m, 1H), 2.49 - 2.40 (m, $J=11.7, 11.7$ Hz, 2H), 2.37 - 2.34 (m, 3H), 2.30 - 2.20 (m, 1H), 2.11 - 2.00 (m, 1H), 1.90 - 1.78 (m, 2H), 1.47 - 1.23 (m, 6H) hLPA1 $\text{IC}_{50} = 283$ nM	Example 10

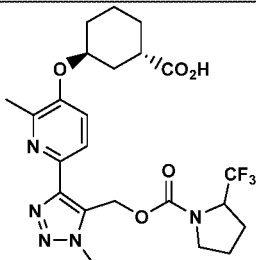
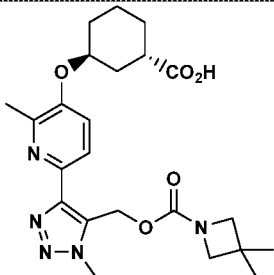
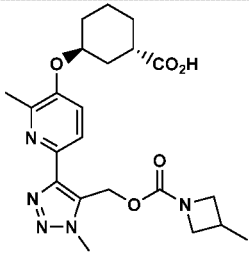
Example	Structure & Name	Analytical & Biology Data	Method
142	 (1S,3S)-3-((6-(5-(((cyclopropyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 444$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.47 (br d, $J=8.2$ Hz, 1H), 5.65 (s, 2H), 4.81 - 4.73 (m, 1H), 4.10 (s, 3H), 3.72 - 3.52 (m, 1H), 2.74 (br s, 3H), 2.65 - 2.57 (m, 1H), 2.41 (s, 3H), 2.04 - 1.94 (m, 1H), 1.92 - 1.70 (m, 3H), 1.68 - 1.41 (m, 4H), 0.57 (br s, 2H), 0.48 (br s, 2H) hLPA1 $IC_{50} = 252$ nM	Example 10
143	 (1S,3S)-3-((6-(5-(((3,3-difluoropyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 480$ 1H NMR (500 MHz, DMSO-d_6) δ 7.82 (br d, $J=7.6$ Hz, 1H), 7.49 (br d, $J=7.6$ Hz, 1H), 5.70 (s, 2H), 4.75 (br s, 1H), 4.09 (s, 3H), 3.73 - 3.54 (m, 1H), 2.42 - 2.38 (m, 3H), 2.38 - 2.31 (m, 2H), 1.99 - 1.46 (m, 8H), 1.23 (s, 2H) hLPA1 $IC_{50} = 518$ nM	Example 1
144	 (1S,3S)-3-((6-(5-(((5-azaspiro[2.4]heptane-5-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 470$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.4$ Hz, 1H), 7.47 (d, $J=8.6$ Hz, 1H), 5.67 (s, 2H), 4.77 (br s, 1H), 4.09 (br s, 3H), 2.72 - 2.60 (m, 1H), 2.43 (s, 3H), 2.08 - 1.97 (m, 1H), 1.83 (br d, $J=10.9$ Hz, 3H), 1.75 - 1.45 (m, 7H), 1.25 (s, 2H), 0.63 - 0.44 (m, 4H) hLPA1 $IC_{50} = 89$ nM	Example 1

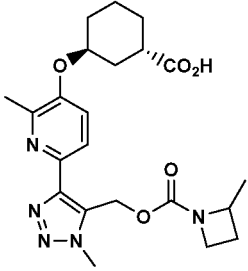
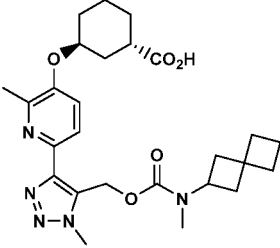
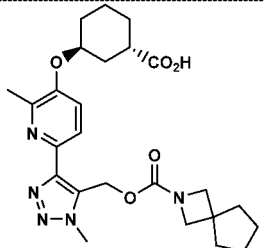
Example	Structure & Name	Analytical & Biology Data	Method
145	 (1S,3S)-3-((6-(5-((((3,3-difluorocyclobutyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 508$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.46 (d, $J=8.7$ Hz, 1H), 5.65 (br s, 2H), 4.77 (br s, 1H), 4.10 (s, 3H), 2.79 (br s, 3H), 2.70 - 2.62 (m, 1H), 2.43 (s, 3H), 2.39 - 2.19 (m, 4H), 2.09 - 1.97 (m, 2H), 1.92 - 1.76 (m, 3H), 1.71 - 1.60 (m, 2H), 1.59 - 1.47 (m, 2H), 1.25 (s, 2H) hLPA1 $\text{IC}_{50} = 94$ nM	Example 3
146	 (1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(spiro[2.3]hexan-1-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (cis isomer from epimerization in final ester hydrolysis)	LCMS, $[M+H]^+ = 484$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.2$ Hz, 1H), 7.51 (d, $J=8.5$ Hz, 1H), 5.98 - 5.48 (m, 2H), 4.45 - 4.36 (m, 1H), 4.13 (s, 3H), 3.53 - 3.14 (m, 1H), 2.72 (s, 2H), 2.47 - 2.39 (m, 1H), 2.35 (s, 3H), 2.27 - 2.20 (m, 1H), 2.08 - 1.99 (m, 1H), 1.93 - 1.58 (m, 7H), 1.50 - 1.20 (m, 6H), 0.75 - 0.65 (m, 1H), 0.58 - 0.50 (m, 1H) hLPA1 $\text{IC}_{50} = 1816$ nM	Example 3

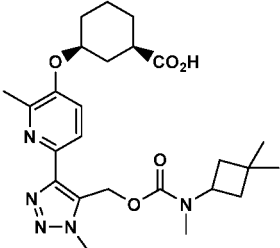
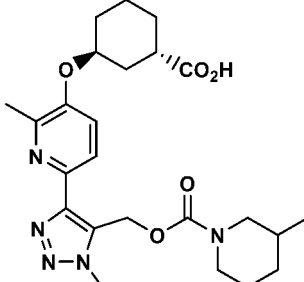
Example	Structure & Name	Analytical & Biology Data	Method
147	 (1S,3S)-3-((2-methyl-6-((1-methyl-5-(((3-methylpyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 458$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.6$ Hz, 1H), 7.47 (d, $J=8.7$ Hz, 1H), 5.65 (s, 2H), 4.81 - 4.74 (m, 1H), 4.08 (s, 3H), 3.82 - 3.59 (m, 1H), 3.45 - 3.10 (m, 3H), 2.81 - 2.66 (m, 1H), 2.65 - 2.58 (m, 1H), 2.41 (s, 3H), 2.08 - 1.95 (m, 1H), 1.93 - 1.73 (m, 4H), 1.67 - 1.33 (m, 5H), 1.26 - 1.18 (m, 1H), 0.99 - 0.86 (m, 3H) hLPA1 $IC_{50} = 250$ nM	Example 1
148	 (1S,3S)-3-((6-(5-(((2-azabicyclo[2.2.1]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 470$ 1H NMR (500 MHz, DMSO-d_6) δ 7.85 - 7.78 (m, 1H), 7.46 (d, $J=8.7$ Hz, 1H), 5.67 - 5.54 (m, 2H), 4.77 (br s, 1H), 4.13 - 4.03 (m, 3H), 3.98 - 3.85 (m, 1H), 3.77 - 3.66 (m, 1H), 3.20 - 3.05 (m, 1H), 2.93 - 2.77 (m, 1H), 2.66 - 2.57 (m, 1H), 2.48 - 2.42 (m, 1H), 2.40 (s, 3H), 2.04 - 1.96 (m, 1H), 1.88 - 1.72 (m, 3H), 1.65 - 1.52 (m, 4H), 1.50 - 1.44 (m, 2H), 1.37 - 1.24 (m, 3H) hLPA1 $IC_{50} = 325$ nM	Example 1

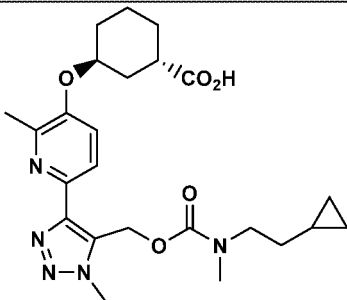
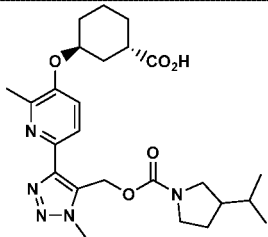
Example	Structure & Name	Analytical & Biology Data	Method
149	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((octahydrocyclopenta[b]pyrrole-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 484$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.47 (br d, $J=8.5$ Hz, 1H), 5.68 - 5.57 (m, 2H), 4.78 (br s, 1H), 4.13 - 4.06 (m, 3H), 4.04 - 3.86 (m, 1H), 3.58 - 3.47 (m, 3H), 2.68 - 2.57 (m, 2H), 2.41 (s, 3H), 2.05 - 1.96 (m, 1H), 1.89 - 1.74 (m, 4H), 1.69 - 1.59 (m, 3H), 1.54 - 1.45 (m, 4H), 1.26 - 1.22 (m, 2H) hLPA1 $IC_{50} = 180$ nM	Example 1
150	 (1S,3S)-3-((6-(5-(((3-(cyclopropylmethyl)pyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 498$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.2$ Hz, 1H), 7.48 (br d, $J=8.5$ Hz, 1H), 5.66 (br s, 2H), 4.82 - 4.75 (m, 1H), 4.09 (s, 3H), 3.63 - 3.33 (m, 1H), 3.32 - 3.08 (m, 2H), 2.97 - 2.72 (m, 1H), 2.68 - 2.60 (m, 1H), 2.42 (s, 3H), 2.20 - 2.08 (m, 1H), 2.07 - 1.98 (m, 1H), 1.98 - 1.90 (m, 1H), 1.90 - 1.73 (m, 3H), 1.68 - 1.38 (m, 5H), 1.29 - 1.11 (m, 2H), 0.70 - 0.54 (m, 1H), 0.42 - 0.30 (m, 2H), 0.04 - -0.11 (m, 2H) hLPA1 $IC_{50} = 91$ nM	Example 1

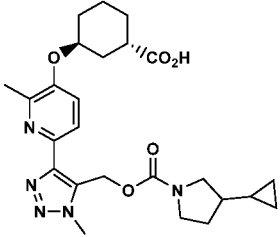
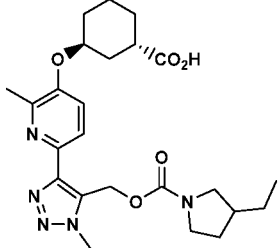
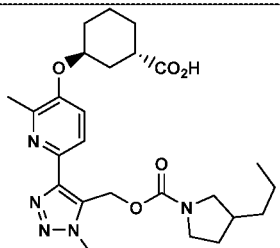
Example	Structure & Name	Analytical & Biology Data	Method
151	 (1S,3S)-3-((6-(5-(((3-isobutylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 500$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.2$ Hz, 1H), 7.47 (br d, $J=8.3$ Hz, 1H), 5.66 (br s, 2H), 4.80 - 4.74 (m, 1H), 4.10 (s, 3H), 3.64 - 3.33 (m, 1H), 2.86 - 2.77 (m, 1H), 2.74 - 2.64 (m, 1H), 2.43 (s, 3H), 2.16 - 2.08 (m, 1H), 2.08 - 2.00 (m, 1H), 1.98 - 1.77 (m, 5H), 1.71 - 1.32 (m, 7H), 1.29 - 1.12 (m, 2H), 0.92 - 0.81 (m, 6H) hLPA1 $\text{IC}_{50} = 101$ nM	Example 1
152	 (1S,3S)-3-((6-(5-(((2-ethylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 471$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br s, 1H), 7.48 (br d, $J=8.5$ Hz, 1H), 5.64 (br s, 2H), 4.79 (br s, 1H), 4.09 (br s, 3H), 3.61 - 3.12 (m, 3H), 2.67 - 2.59 (m, 1H), 2.42 (s, 3H), 2.06 - 1.94 (m, 1H), 1.92 - 1.42 (m, 12H), 0.86 - 0.75 (m, 2H), 0.64 - 0.54 (m, 1H) hLPA1 $\text{IC}_{50} = 157$ nM	Example 1
153	 (1S,3S)-3-((6-(5-(((2-isobutylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 500$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.48 (br d, $J=7.3$ Hz, 1H), 5.74 - 5.48 (m, 2H), 4.78 (br s, 1H), 4.10 (br s, 3H), 3.66 - 3.11 (m, 3H), 2.41 (br s, 3H), 2.09 - 1.41 (m, 14H), 1.36 - 1.07 (m, 2H), 0.89 (br s, 3H), 0.59 - 0.42 (m, 3H) hLPA1 $\text{IC}_{50} = 163$ nM	Example 1

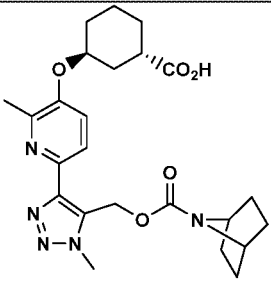
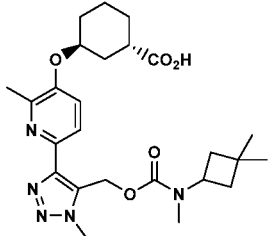
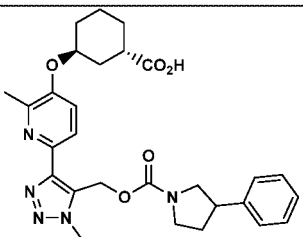
Example	Structure & Name	Analytical & Biology Data	Method
154	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((2-(trifluoromethyl)pyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 511$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.2$ Hz, 1H), 7.55 (br d, $J=8.5$ Hz, 1H), 5.82 - 5.65 (m, 2H), 4.78 - 4.68 (m, 1H), 4.10 (br s, 3H), 3.29 - 3.13 (m, 3H), 2.39 (s, 2H), 2.14 - 2.00 (m, 1H), 1.98 - 1.46 (m, 12H) hLPA1 $\text{IC}_{50} = 321$ nM	Example 1
155	 (1S,3S)-3-((6-(5-(((3,3-dimethylazetidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 458$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.2$ Hz, 1H), 7.49 (d, $J=8.9$ Hz, 1H), 5.64 (s, 2H), 4.79 (br s, 1H), 4.07 (s, 3H), 3.64-3.45 (m, 1H), 3.32-3.09 (m, 1H), 2.70-2.59 (m, 1H), 2.43 (s, 3H), 2.30 - 2.15 (m, 1H), 2.05 - 1.98 (m, 1H), 1.91-1.73 (m, 3H), 1.67-1.45 (m, 4H), 1.16 (s, 6H) hLPA1 $\text{IC}_{50} = 175$ nM	Example 1
156	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-methylazetidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 444$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.48 (br d, $J=8.9$ Hz, 1H), 5.64 (s, 2H), 4.79 (br s, 1H), 4.07 (s, 3H), 4.00 - 3.92 (m, 2H), 3.31 - 3.09 (m, 1H), 2.68 - 2.58 (m, 2H), 2.43 (s, 3H), 2.02 (br d, $J=13.4$ Hz, 1H), 1.94 - 1.73 (m, 3H), 1.63 (br d, $J=10.1$ Hz, 4H), 1.12 (d, $J=6.7$ Hz, 3H) hLPA1 $\text{IC}_{50} = 231$ nM	Example 1

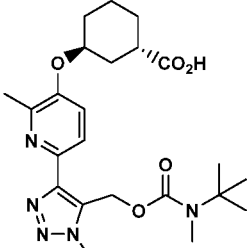
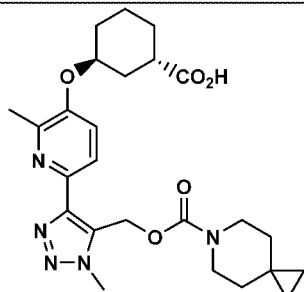
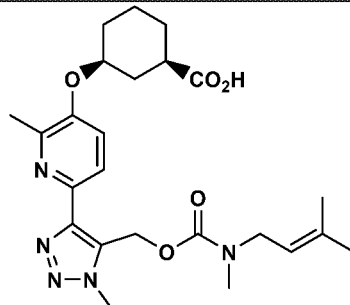
Example	Structure & Name	Analytical & Biology Data	Method
157	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((2-methylazetidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridine-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 444$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.9$ Hz, 1H), 5.63 (s, 2H), 4.79 (br s, 1H), 4.08 (s, 3H), 3.81 - 3.69 (m, 2H), 3.64 - 3.50 (m, 1H), 3.31 - 3.10 (m, 1H), 2.67 - 2.59 (m, 1H), 2.43 (s, 3H), 2.33 - 2.21 (m, 1H), 2.12 - 1.96 (m, 1H), 1.64 (br s, 7H), 1.00 (d, $J=6.1$ Hz, 3H) hLPA1 $IC_{50} = 529$ nM	Example 1
158	 (1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(spiro[3.3]heptan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridine-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 498$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.2$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.62 (br s, 2H), 4.78 (br s, 1H), 4.09 (s, 3H), 3.32 - 3.12 (m, 1H), 2.74 - 2.58 (m, 4H), 2.41 (s, 3H), 2.10 - 1.70 (m, 14H), 1.68 - 1.44 (m, 4H) hLPA1 $IC_{50} = 32$ nM	Example 10
159	 (1S,3S)-3-((6-(5-(((2-azaspiro[3.4]octane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridine-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.64 (s, 2H), 4.78 (br s, 1H), 4.07 (s, 3H), 3.69 (br s, 3H), 3.63 - 3.51 (m, 1H), 3.31 - 3.11 (m, 2H), 2.42 (s, 3H), 1.91 - 1.77 (m, 3H), 1.71 - 1.58 (m, 6H), 1.57 - 1.47 (m, 6H) hLPA1 $IC_{50} = 162$ nM	Example 1

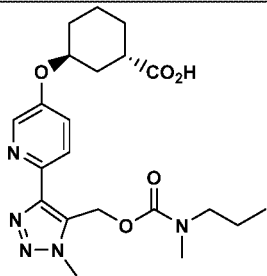
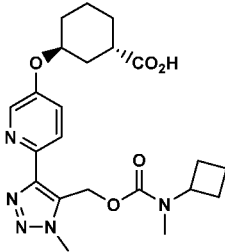
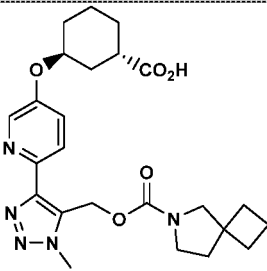
Example	Structure & Name	Analytical & Biology Data	Method
160	 (1R,3S)-3-((6-(5-(((3,3-dimethylcyclobutyl)(methyl)carbamoyloxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (cis isomer from epimerization in final ester hydrolysis step)	LCMS, $[M+H]^+ = 486$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.53 (d, $J=8.5$ Hz, 1H), 5.63 (br s, 2H), 4.49 - 4.36 (m, 1H), 4.10 (s, 3H), 2.77 - 2.69 (m, 3H), 2.48 - 2.39 (m, 1H), 2.37 (s, 3H), 2.31 - 2.23 (m, 1H), 2.12 - 2.02 (m, 1H), 1.92 - 1.59 (m, 6H), 1.50 - 1.20 (m, 4H), 1.14 - 0.95 (m, 6H) hLPA1 $IC_{50} = 61$ nM	Example 3
161	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-methylpiperidine-1-carbonyloxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 472$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.46 (d, $J=8.7$ Hz, 1H), 5.65 (s, 2H), 4.77 (br s, 1H), 4.09 (s, 3H), 3.81 - 3.66 (m, 1H), 2.82 - 2.70 (m, 1H), 2.69 - 2.62 (m, 1H), 2.43 (s, 3H), 2.06 - 1.97 (m, 1H), 1.92 - 1.76 (m, 3H), 1.66 (br s, 6H), 1.46 - 1.18 (m, 3H), 1.03 (s, 2H), 0.86 - 0.71 (m, 3H) hLPA1 $IC_{50} = 178$ nM	Example 1

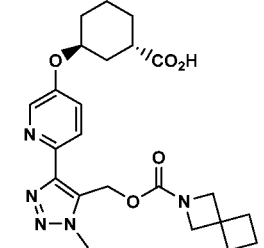
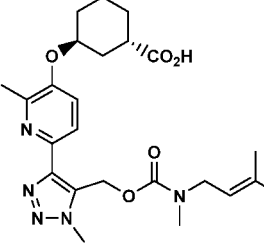
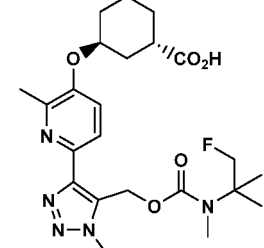
Example	Structure & Name	Analytical & Biology Data	Method
162	 (1S,3S)-3-((6-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.6$ Hz, 1H), 7.45 (d, $J=8.6$ Hz, 1H), 5.63 (s, 2H), 4.82 - 4.71 (m, 1H), 4.09 (s, 3H), 3.62 - 3.53 (m, 2H), 3.34 - 3.18 (m, 1H), 2.79 (br s, 3H), 2.70 - 2.61 (m, 1H), 2.42 (s, 3H), 2.07 - 1.97 (m, 1H), 1.89 - 1.77 (m, 3H), 1.70 - 1.47 (m, 4H), 1.31 - 1.15 (m, 2H), 0.42 - 0.16 (m, 2H), 0.03 - -0.26 (m, 2H) hLPA1 $\text{IC}_{50} = 34$ nM	Example 1
163	 (1S,3S)-3-((6-(5-(((3-isopropylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 486$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.66 (br d, $J=9.5$ Hz, 2H), 4.83 - 4.75 (m, 1H), 4.10 (s, 3H), 3.18 (br s, 1H), 2.93 - 2.81 (m, 1H), 2.74 (s, 1H), 2.68 - 2.60 (m, 1H), 2.42 (s, 3H), 2.07 - 1.98 (m, 1H), 1.94 - 1.73 (m, 6H), 1.67 - 1.34 (m, 6H), 0.93 - 0.75 (m, 6H) hLPA1 $\text{IC}_{50} = 104$ nM	Example 1

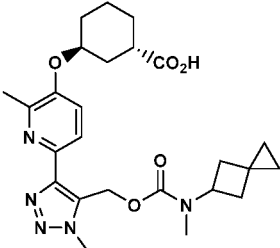
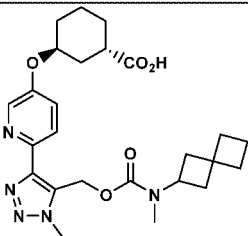
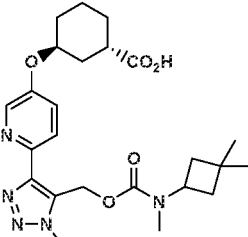
Example	Structure & Name	Analytical & Biology Data	Method
164	 (1S,3S)-3-((6-(5-(((3-cyclopropylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 484$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.82 (br d, $J=8.5$ Hz, 1H), 7.46 (d, $J=8.5$ Hz, 1H), 5.65 (br s, 2H), 4.80 - 4.74 (m, 1H), 4.08 (s, 3H), 3.33 - 3.08 (m, 2H), 2.88 (s, 2H), 2.65 - 2.58 (m, 1H), 2.40 (s, 3H), 2.04 - 1.95 (m, 1H), 1.90 (s, 4H), 1.62 (br s, 6H), 0.71 - 0.54 (m, 1H), 0.42 - 0.26 (m, 2H), 0.16 - 0.02 (m, 2H) hLPA1 $\text{IC}_{50} = 83$ nM	Example 1
165	 (1S,3S)-3-((6-(5-(((3-ethylpyrrolidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 472$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.49 (d, $J=8.9$ Hz, 1H), 5.67 (br s, 2H), 4.83 - 4.76 (m, 1H), 4.10 (s, 3H), 3.24 - 3.09 (m, 1H), 2.98 - 2.78 (m, 1H), 2.77 - 2.69 (m, 1H), 2.67 - 2.61 (m, 1H), 2.42 (s, 3H), 2.06 - 1.79 (m, 6H), 1.67 - 1.23 (m, 8H), 0.93 - 0.79 (m, 3H) hLPA1 $\text{IC}_{50} = 102$ nM	Example 1
166	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-propylpyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 486$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.66 (br s, 2H), 4.82 - 4.74 (m, 1H), 4.09 (s, 3H), 3.24 - 3.07 (m, 1H), 2.90 (s, 1H), 2.76 - 2.67 (m, 1H), 2.67 - 2.60 (m, 1H), 2.42 (s, 3H), 2.10 - 1.97 (m, 2H), 1.92 (s, 5H), 1.68 - 1.34 (m, 5H), 1.32 - 1.19 (m, 4H), 0.92 - 0.80 (m, 3H) hLPA1 $\text{IC}_{50} = 109$ nM	Example 1

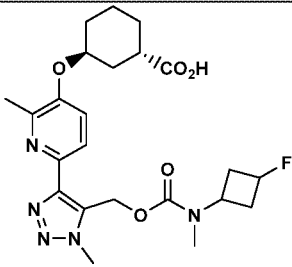
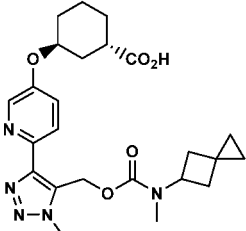
Example	Structure & Name	Analytical & Biology Data	Method
167	 (1S,3S)-3-(((6-(5-(((7-azabicyclo[2.2.1]heptane-7-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 470$ 1H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, $J=8.5$ Hz, 1H), 7.50 (d, $J=8.5$ Hz, 1H), 5.64 (s, 2H), 4.79 (br s, 1H), 4.09 (s, 3H), 3.31 - 3.13 (m, 1H), 2.67 - 2.59 (m, 1H), 2.42 (s, 3H), 2.06 - 1.98 (m, 1H), 1.91 - 1.74 (m, 3H), 1.67 - 1.46 (m, 8H), 1.39 - 1.33 (m, 4H) hLPA1 $IC_{50} = 317$ nM	Example 1
168	 (1S,3S)-3-(((6-(5-(((3,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 486$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.63 (br s, 2H), 4.78 (br s, 1H), 4.10 (s, 3H), 2.72 (br s, 3H), 2.68 - 2.58 (m, 1H), 2.41 (s, 3H), 2.00 (br s, 1H), 1.93 - 1.71 (m, 6H), 1.64 (br s, 5H), 1.07 - 0.95 (m, 6H) hLPA1 $IC_{50} = 29$ nM	Example 3
169	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((3-phenylpyrrolidine-1-carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 520$ 1H NMR (500 MHz, DMSO-d_6) δ 7.91 - 7.81 (m, 1H), 7.52 - 7.45 (m, 1H), 7.37 - 7.19 (m, 5H), 5.72 (br s, 2H), 4.83 - 4.75 (m, 1H), 4.11 (br d, $J=13.7$ Hz, 3H), 3.81 - 3.63 (m, 1H), 3.39 - 3.10 (m, 3H), 2.67 - 2.61 (m, 1H), 2.43 (br d, $J=4.9$ Hz, 3H), 2.24 - 2.16 (m, 1H), 2.07 - 1.99 (m, 1H), 1.97 - 1.73 (m, 4H), 1.70 - 1.47 (m, 4H) hLPA1 $IC_{50} = 336$ nM	Example 1

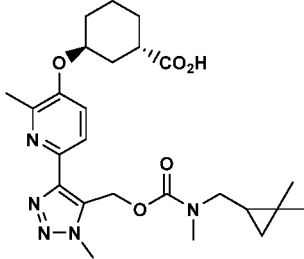
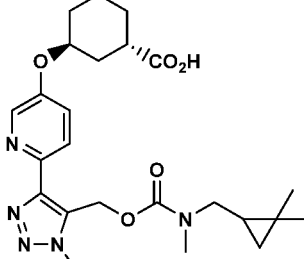
Example	Structure & Name	Analytical & Biology Data	Method
170	 (1S,3S)-3-((6-(5-(((tert-butyl (methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 460$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.48 (br d, $J=8.5$ Hz, 1H), 5.60 (s, 2H), 4.79 (br s, 1H), 4.10 (s, 3H), 2.77 (s, 3H), 2.68 - 2.58 (m, 1H), 2.42 (s, 3H), 2.09 - 1.97 (m, 1H), 1.93 - 1.73 (m, 3H), 1.69 - 1.43 (m, 4H), 1.27 (s, 9H) hLPA1 $\text{IC}_{50} = 183$ nM	Example 1
171	 (1S,3S)-3-((6-(5-(((6-azaspiro [2.5]octane-6-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 5.66 (s, 2H), 4.79 (br s, 1H), 4.09 (s, 3H), 3.59 - 3.16 (m, 2H), 2.69 - 2.60 (m, 1H), 2.42 (s, 3H), 2.06 - 1.95 (m, 1H), 1.91 - 1.71 (m, 3H), 1.68 - 1.44 (m, 4H), 1.31 - 1.11 (m, 4H), 0.28 (s, 4H) hLPA1 $\text{IC}_{50} = 162$ nM	Example 1
172	 (1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(3-methylbut-2-en-1-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (cis isomer from epimerization during final hydrolysis step)	LCMS, $[M+H]^+ = 472$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.53 (d, $J=8.5$ Hz, 1H), 5.68 - 5.59 (m, 2H), 5.16 - 4.91 (m, 1H), 4.47 - 4.36 (m, 1H), 4.09 (s, 3H), 3.87 - 3.60 (m, 2H), 2.80 - 2.64 (m, 3H), 2.45 - 2.39 (m, 1H), 2.37 (s, 3H), 2.30 - 2.22 (m, 1H), 2.09 - 2.02 (m, 1H), 1.93 - 1.78 (m, 3H), 1.72 - 1.49 (m, 4H), 1.47 - 1.28 (m, 5H) hLPA1 $\text{IC}_{50} = 312$ nM	Example 3

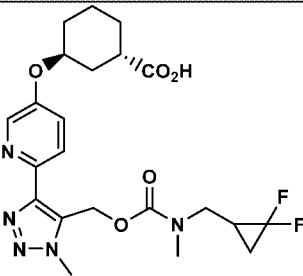
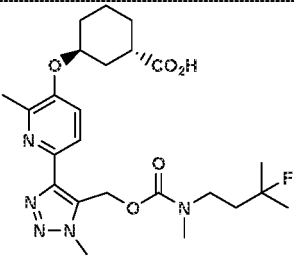
Example	Structure & Name	Analytical & Biology Data	Method
173	 (1S,3S)-3-((6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 432$ 1H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, $J=2.4$ Hz, 1H), 7.99 (br d, $J=8.2$ Hz, 1H), 7.58 - 7.52 (m, 1H), 5.67 - 5.58 (m, 2H), 4.79 (br s, 1H), 4.10 (s, 3H), 3.20 - 3.01 (m, 2H), 2.77 (br d, $J=15.9$ Hz, 3H), 2.71 - 2.62 (m, 1H), 2.00 - 1.72 (m, 4H), 1.72 - 1.41 (m, 5H), 1.40 - 1.28 (m, 1H), 0.86 - 0.61 (m, 3H) hLPA1 $IC_{50} = 131$ nM	Example 1
174	 (1S,3S)-3-((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 444$ 1H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, $J=2.4$ Hz, 1H), 8.00 (d, $J=8.9$ Hz, 1H), 7.55 (dd, $J=8.9, 2.7$ Hz, 1H), 5.63 (s, 2H), 4.79 (br s, 1H), 4.57 - 4.17 (m, 1H), 4.10 (s, 3H), 2.80 - 2.63 (m, 4H), 2.12 - 1.94 (m, 4H), 1.90 - 1.74 (m, 4H), 1.72 - 1.48 (m, 5H) hLPA1 $IC_{50} = 58$ nM	Example 1
175	 (1S,3S)-3-((6-(5-(((6-azaspiro[3.4]octane-6-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 470$ 1H NMR (500 MHz, DMSO-d_6) δ 8.43 - 8.26 (m, 1H), 8.08 - 7.91 (m, 1H), 7.64 - 7.44 (m, 1H), 5.63 (br s, 2H), 4.78 (br s, 1H), 4.08 (br s, 3H), 3.30 - 3.11 (m, 3H), 2.71 - 2.60 (m, 1H), 2.00 - 1.88 (m, 2H), 1.88 - 1.73 (m, 9H), 1.70 - 1.44 (m, 4H) hLPA1 $IC_{50} = 703$ nM	Example 1

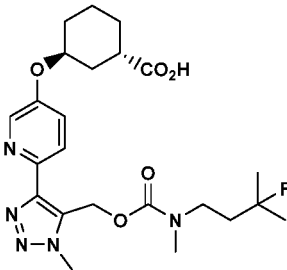
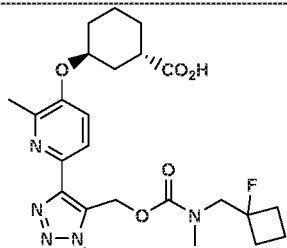
Example	Structure & Name	Analytical & Biology Data	Method
176	 (1S,3S)-3-((6-(5-(((2-azaspiro[3.3]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 456$ 1H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, $J=2.4$ Hz, 1H), 8.00 (d, $J=8.9$ Hz, 1H), 7.55 (dd, $J=8.7, 2.6$ Hz, 1H), 5.60 (s, 2H), 4.79 (br s, 1H), 4.08 (s, 3H), 3.84 (s, 4H), 2.72 - 2.63 (m, 1H), 2.13 - 2.02 (m, 4H), 2.01 - 1.92 (m, 1H), 1.90 - 1.76 (m, 3H), 1.76 - 1.60 (m, 4H), 1.60 - 1.48 (m, 2H) hLPA1 $IC_{50} = 400$ nM	Example 1
177	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(3-methylbut-2-en-1-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472$ 1H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, $J=8.5$ Hz, 1H), 7.49 (d, $J=8.5$ Hz, 1H), 5.69 - 5.61 (m, 2H), 5.17 - 4.91 (m, 1H), 4.78 (br s, 1H), 4.09 (s, 3H), 3.85 - 3.61 (m, 2H), 2.80 - 2.66 (m, 3H), 2.65 - 2.59 (m, 1H), 2.41 (s, 3H), 2.06 - 1.96 (m, 1H), 1.90 - 1.74 (m, 3H), 1.73 - 1.60 (m, 4H), 1.59 - 1.47 (m, 4H), 1.46 - 1.37 (m, 2H) hLPA1 $IC_{50} = 21$ nM	Example 3
178	 (1S,3S)-3-((6-(5-(((1-fluoro-2-methylpropan-2-yl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 478$ 1H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, $J=8.5$ Hz, 1H), 7.49 (d, $J=8.5$ Hz, 1H), 5.62 (s, 2H), 4.81 - 4.74 (m, 1H), 4.57 (s, 1H), 4.47 (s, 1H), 4.11 (s, 3H), 2.82 (s, 3H), 2.65 - 2.58 (m, 1H), 2.42 (s, 3H), 2.05 - 1.96 (m, 1H), 1.89 - 1.74 (m, 3H), 1.64 (br s, 4H), 1.28 (br s, 6H) hLPA1 $IC_{50} = 156$ nM	Example 3

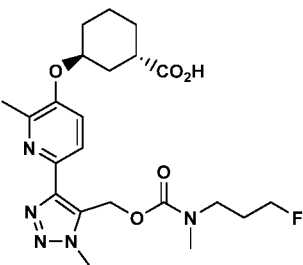
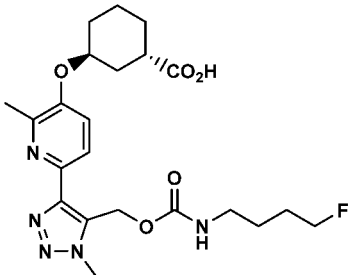
Example	Structure & Name	Analytical & Biology Data	Method
179	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(spiro[2.3]hexan-5-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484$ 1H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, $J=8.5$ Hz, 1H), 7.45 (d, $J=8.6$ Hz, 1H), 5.63 (s, 2H), 4.75 (br s, 1H), 4.09 (s, 3H), 2.88 - 2.72 (m, 3H), 2.70 - 2.59 (m, 1H), 2.41 (s, 3H), 2.38 - 2.28 (m, 2H), 2.08 - 1.75 (m, 7H), 1.70 - 1.45 (m, 4H), 0.47 - 0.26 (m, 4H) hLPA1 $IC_{50} = 14$ nM	Example 3
180	 (1S,3S)-3-((6-(1-methyl-5-(((methyl(spiro[3.3]heptan-2-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484$ 1H NMR (500 MHz, DMSO-d_6) δ 8.34 (br s, 1H), 7.99 (br d, $J=8.9$ Hz, 1H), 7.59 - 7.51 (m, 1H), 5.60 (br s, 2H), 4.82 - 4.74 (m, 1H), 4.09 (s, 3H), 2.72 - 2.61 (m, 4H), 2.05 - 1.70 (m, 15H), 1.70 - 1.60 (m, 2H), 1.60 - 1.44 (m, 2H) hLPA1 $IC_{50} = 62$ nM	Example 10
181	 (1S,3S)-3-((6-(5-(((3,3-dimethylcyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472$ 1H NMR (500 MHz, DMSO-d_6) δ 8.34 (br d, $J=2.1$ Hz, 1H), 7.98 (br d, $J=8.5$ Hz, 1H), 7.54 (dd, $J=8.9$, 2.7 Hz, 1H), 5.60 (br s, 2H), 4.78 (br s, 1H), 4.61 - 4.23 (m, 1H), 4.10 (s, 3H), 2.71 (s, 3H), 2.68 - 2.61 (m, 1H), 2.08 - 1.71 (m, 7H), 1.66 (br d, $J=8.9$ Hz, 2H), 1.60 - 1.46 (m, 2H), 1.14 - 0.90 (m, 6H) hLPA1 $IC_{50} = 101$ nM	Example 10

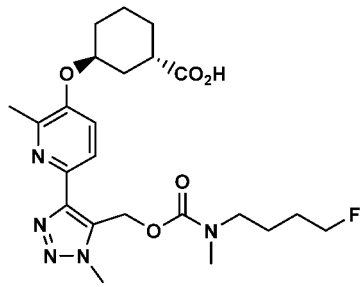
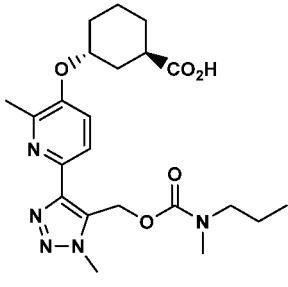
Example	Structure & Name	Analytical & Biology Data	Method
182	 (1S,3S)-3-(((6-(5-(((3-fluorocyclobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 476$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.5$ Hz, 1H), 7.46 (d, $J=8.6$ Hz, 1H), 5.63 (s, 2H), 5.17 - 4.99 (m, 1H), 4.79 - 4.71 (m, 1H), 4.09 (s, 3H), 3.69 - 3.51 (m, 1H), 3.46 (br s, 1H), 2.75 (s, 3H), 2.67 - 2.57 (m, 1H), 2.41 (s, 4H), 2.32 - 2.17 (m, 2H), 2.03 - 1.95 (m, 1H), 1.88 - 1.75 (m, 3H), 1.69 - 1.45 (m, 4H) hLPA1 $IC_{50} = 61$ nM	Example 10
183	 (1S,3S)-3-(((6-(1-methyl-5-(((methyl(spiro[2.3]hexan-5-yl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 470$ 1H NMR (500 MHz, CHLOROFORM-d) δ 8.34 (d, $J=2.5$ Hz, 1H), 8.13 (d, $J=8.8$ Hz, 1H), 7.36 (dd, $J=8.8, 2.8$ Hz, 1H), 5.76 (s, 2H), 4.79 - 4.69 (m, 1H), 4.16 (s, 3H), 3.01 - 2.82 (m, 4H), 2.47 - 2.32 (m, 2H), 2.18 - 1.87 (m, 7H), 1.85 - 1.56 (m, 4H), 0.61 - 0.27 (m, 4H) hLPA1 $IC_{50} = 20$ nM	Example 3

Example	Structure & Name	Analytical & Biology Data	Method
184	 (1S,3S)-3-((6-(5-((((2,2-dimethylcyclopropyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 486$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.94 - 7.76 (m, 1H), 7.55 - 7.40 (m, 1H), 5.75 - 5.53 (m, 2H), 4.77 (br s, 1H), 4.09 (s, 3H), 3.30 - 3.02 (m, 1H), 2.90 - 2.72 (m, 3H), 2.70 - 2.58 (m, 1H), 2.45 - 2.32 (m, 3H), 2.06 - 1.94 (m, 1H), 1.90 - 1.72 (m, 3H), 1.67 - 1.43 (m, 4H), 1.08 - 0.93 (m, 3H), 0.92 - 0.77 (m, 3H), 0.75 - 0.49 (m, 1H), 0.46 - 0.14 (m, 1H), 0.14 to -0.15 (m, 1H) hLPA1 $\text{IC}_{50} = 37$ nM	Example 3
185	 (1S,3S)-3-((6-(5-((((2,2-dimethylcyclopropyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 472$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.34 (br s, 1H), 7.99 (br d, $J=8.7$ Hz, 1H), 7.53 (dd, $J=8.6$, 2.5 Hz, 1H), 5.63 (s, 2H), 4.84 - 4.73 (m, 1H), 4.11 (s, 3H), 2.82 (br s, 3H), 2.73 - 2.63 (m, 1H), 2.03 - 1.93 (m, 1H), 1.91 - 1.74 (m, 3H), 1.72 - 1.49 (m, 4H), 1.26 (s, 1H), 0.97 (br s, 6H), 0.66 (br s, 1H), 0.38 (br s, 1H), 0.02 (br s, 1H) hLPA1 $\text{IC}_{50} = 86$ nM	Example 3

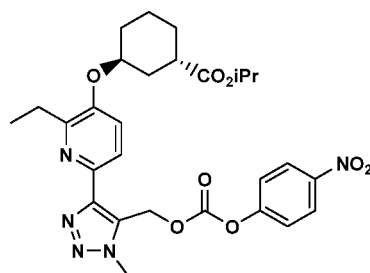
Example	Structure & Name	Analytical & Biology Data	Method
186	 (1S,3S)-3-(((6-(5-((((2,2-difluorocyclopropyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (mixture of diastereomers)	LCMS, $[M+H]^+ = 480$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.34 (d, $J=2.3$ Hz, 1H), 7.99 (d, $J=8.7$ Hz, 1H), 7.53 (dd, $J=8.7, 2.7$ Hz, 1H), 5.64 (br s, 2H), 4.82 - 4.73 (m, 1H), 4.10 (s, 3H), 2.83 (br s, 3H), 2.72 - 2.64 (m, 1H), 2.01 - 1.93 (m, 1H), 1.90 - 1.73 (m, 4H), 1.71 - 1.48 (m, 5H), 1.25 (s, 1H), 1.23 - 1.09 (m, 1H) hLPA1 $\text{IC}_{50} = 67$ nM	Example 3
187	 (1S,3S)-3-(((6-(5-((((3-fluoro-3-methylbutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 492$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.90 - 7.73 (m, 1H), 7.51 - 7.42 (m, 1H), 5.64 - 5.58 (m, 2H), 4.76 (br s, 1H), 4.08 (br s, 3H), 3.81 - 3.74 (m, 2H), 3.31 - 3.22 (m, 1H), 3.15 - 3.09 (m, 1H), 2.66 - 2.57 (m, 1H), 2.38 (br s, 3H), 1.98 - 1.72 (m, 5H), 1.67 - 1.39 (m, 6H), 1.32 - 1.24 (m, 3H), 1.09 - 1.01 (m, 3H) hLPA1 $\text{IC}_{50} = 50$ nM	Example 3

Example	Structure & Name	Analytical & Biology Data	Method
188	 (1S,3S)-3-((6-(5-(((3-fluoro-3-methylbutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 478$ ^1H NMR (500 MHz, DMSO-d_6) δ 8.39 - 8.25 (m, 1H), 8.08 - 7.93 (m, 1H), 7.54 (br s, 1H), 5.66 - 5.53 (m, 2H), 4.76 (br s, 1H), 4.09 (br s, 2H), 3.86 - 3.74 (m, 2H), 3.31 - 3.24 (m, 1H), 3.16 - 3.12 (m, 1H), 2.68 - 2.60 (m, 1H), 1.97 - 1.73 (m, 5H), 1.63 (br s, 6H), 1.33 - 1.25 (m, 3H), 1.14 - 1.07 (m, 3H) hLPA1 $\text{IC}_{50} = 32$ nM	Example 3
189	 (1S,3S)-3-((6-(5-(((1-fluorocyclobutyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 490$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.4$ Hz, 1H), 7.46 (br d, $J=8.6$ Hz, 1H), 5.69 (s, 2H), 4.77 (br s, 1H), 4.11 (s, 3H), 3.72 - 3.23 (m, 1H), 2.85 (br s, 3H), 2.72 - 2.60 (m, 1H), 2.42 (s, 3H), 2.20 - 1.73 (m, 9H), 1.65 (br d, $J=9.8$ Hz, 5H) hLPA1 $\text{IC}_{50} = 120$ nM	Example 3

Example	Structure & Name	Analytical & Biology Data	Method
190	 (1S,3S)-3-(((6-(5-(((3-fluoropropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 464.1$ ^1H NMR (500 MHz, CDCl_3) δ 8.12 (d, $J=8.8$ Hz, 1H), 7.86 (br t, $J=7.8$ Hz, 1H), 5.64 - 5.57 (m, 1H), 5.55 - 5.47 (m, 1H), 4.86 (br s, 1H), 4.53 (dt, $J=10.4, 5.4$ Hz, 1H), 4.43 (dt, $J=10.5, 5.3$ Hz, 1H), 4.22 (s, 3H), 3.45 (q, $J=7.1$ Hz, 2H), 2.97 (d, $J=12.9$ Hz, 3H), 2.88 (br s, 1H), 2.74 (d, $J=2.2$ Hz, 3H), 2.18 - 1.76 (m, 9H), 1.68 (br d, $J=6.3$ Hz, 1H) ^{19}F-NMR: -221.9 ppm hLPA1 $\text{IC}_{50} = 81$ nM	
191	 (1S,3S)-3-(((6-(5-(((4-fluorobutyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 464.1$ ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.84 (d, $J=8.5$ Hz, 1H), 7.48 (d, $J=8.7$ Hz, 1H), 7.33 (br t, $J=5.6$ Hz, 1H), 5.64 (s, 2H), 4.79 (br s, 1H), 4.47 (t, $J=6.1$ Hz, 1H), 4.37 (t, $J=6.0$ Hz, 1H), 4.08 (s, 3H), 3.02 (q, $J=6.0$ Hz, 2H), 2.71 - 2.59 (m, 1H), 2.42 (s, 3H), 2.11 - 1.98 (m, 1H), 1.90 - 1.75 (m, 3H), 1.72 - 1.41 (m, 8H) hLPA1 $\text{IC}_{50} = 553$ nM	

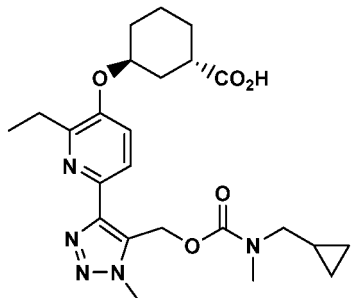
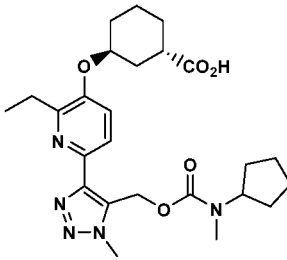
Example	Structure & Name	Analytical & Biology Data	Method
192	 (1S,3S)-3-((6-(5-(((4-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 478.4$ 1H NMR (400 MHz, $CDCl_3$) δ 11.11 (br s, 1H), 8.18 (d, $J=8.8$ Hz, 1H), 8.00 (d, $J=8.8$ Hz, 1H), 5.58 - 5.39 (m, 2H), 4.90 (br s, 1H), 4.57 - 4.49 (m, 1H), 4.46 - 4.35 (m, 1H), 4.23 (d, $J=4.2$ Hz, 3H), 3.35 (br d, $J=7.0$ Hz, 2H), 3.03 - 2.69 (m, 7H), 2.24 - 1.57 (m, 12H) ^{19}F NMR: 219 ppm hLPA1 $IC_{50} = 36$ nM	
193	 (1R,3R)-3-((2-methyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 446.1$ 1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, $J=8.6$ Hz, 1H), 7.20 (d, $J=8.6$ Hz, 1H), 5.77 (br d, $J=5.3$ Hz, 2H), 4.38 - 4.21 (m, 1H), 4.15 (s, 3H), 3.34 - 3.06 (m, 2H), 2.98 - 2.79 (m, 3H), 2.60 - 2.38 (m, 5H), 2.21 - 1.94 (m, 3H), 1.81 - 1.66 (m, 1H), 1.63 - 1.33 (m, 7H), 0.97 - 0.70 (m, 2H) hLPA1 $IC_{50} = 1696$ nM	

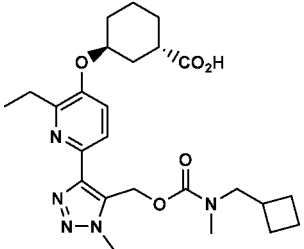
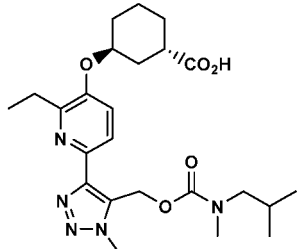
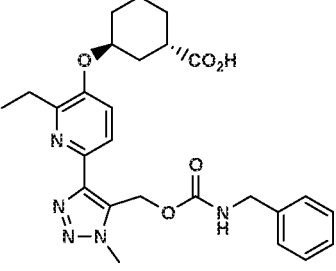
The following analogs were synthesized according to the methods described for the preparation of Example 1 except that the intermediate 3 was used (instead of Example 1F).

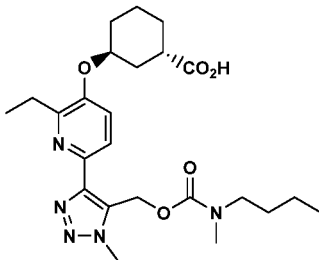
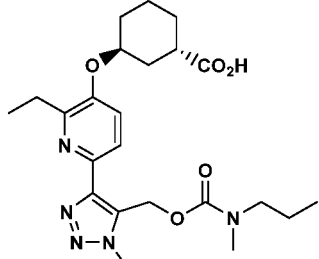


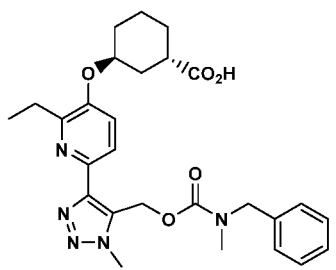
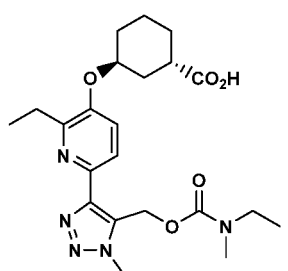
Intermediate 3

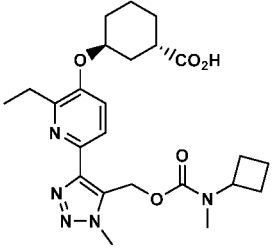
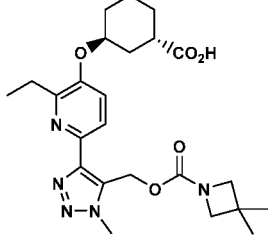
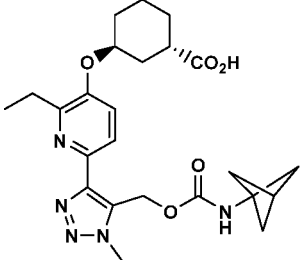
Intermediate 3 was prepared from 2,5-dibromo-6-ethyl-pyridine using the same synthetic sequence as described for the preparation of Example 1.

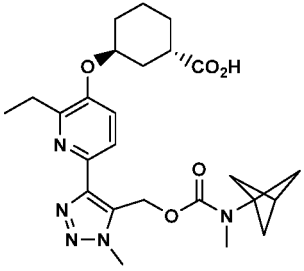
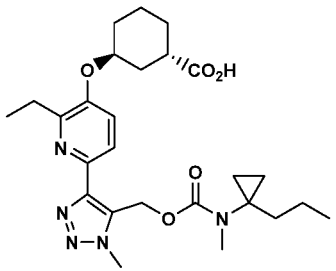
Example	Structure & Name	Analytical & Biology Data	Method
194	 (1S,3S)-3-(((6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.0$ 1H NMR (500 MHz, DMSO-d_6) δ 7.87 (br d, $J=7.9$ Hz, 1H), 7.50 (br d, $J=8.5$ Hz, 1H), 5.69 (br d, $J=16.2$ Hz, 2H), 4.81 (br s, 1H), 4.14 (s, 3H), 3.56 (br s, 1H), 3.10 (br s, 1H), 2.99 (br s, 1H), 2.89 - 2.78 (m, 5H), 2.10 - 2.02 (m, 1H), 1.90 (br d, $J=11.6$ Hz, 1H), 1.86 - 1.78 (m, 2H), 1.69 - 1.48 (m, 4H), 1.31 - 1.20 (m, 3H), 1.03 - 0.86 (m, 1H), 0.85 - 0.66 (m, 1H), 0.45 (br s, 1H), 0.28 (br s, 1H), 0.22 (br s, 1H), 0.00 (br s, 1H) hLPA1 $IC_{50} = 14$ nM	Example 1
195	 (1S,3S)-3-(((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 485.9$ 1H NMR (500 MHz, DMSO-d_6) δ 7.94 - 7.76 (m, 1H), 7.60 - 7.41 (m, 1H), 5.66 (s, 2H), 4.88 - 4.62 (m, 1H), 2.80 (q, $J=7.3$ Hz, 2H), 2.64 (br s, 3H), 2.01 - 1.92 (m, 1H), 1.92 - 1.86 (m, 1H), 1.85 - 1.72 (m, 4H), 1.67 - 1.58 (m, 5H), 1.54 (br s, 5H), 1.43 (br s, 5H), 1.24 (br t, $J=7.4$ Hz, 3H) hLPA1 $IC_{50} = 11$ nM	

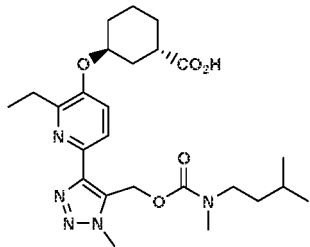
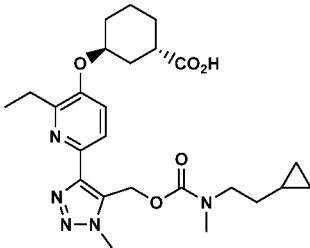
Example	Structure & Name	Analytical & Biology Data	Method
196	 (1S,3S)-3-(((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 486.2$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.2$ Hz, 1H), 7.50 (br d, $J=8.6$ Hz, 1H), 5.66 (br d, $J=16.0$ Hz, 2H), 4.75 (br s, 1H), 4.10 (br d, $J=9.4$ Hz, 3H), 2.80 (br d, $J=6.4$ Hz, 2H), 2.73 (br d, $J=17.7$ Hz, 3H), 1.91 (br d, $J=14.9$ Hz, 2H), 1.84 (s, 6H), 1.76 (s, 4H), 1.71 - 1.57 (m, 4H), 1.54 (br s, 2H), 1.43 (br d, $J=8.1$ Hz, 1H), 1.25 (br d, $J=6.8$ Hz, 3H) hLPA1 $\text{IC}_{50} = 12$ nM	
197	 (1S,3S)-3-((2-ethyl-6-(5-(((isobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 474.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.80 (br t, $J=8.1$ Hz, 1H), 7.45 (br d, $J=8.2$ Hz, 1H), 5.63 (br d, $J=18.3$ Hz, 2H), 4.75 (br s, 1H), 4.08 (br s, 3H), 2.99 (br d, $J=7.0$ Hz, 1H), 2.85 (br d, $J=6.7$ Hz, 1H), 2.81 - 2.70 (m, 5H), 1.97 (br d, $J=13.7$ Hz, 1H), 1.86 (s, 1H), 1.79 (br d, $J=12.5$ Hz, 3H), 1.60 (br d, $J=8.9$ Hz, 3H), 1.57 - 1.45 (m, 2H), 1.23 (br d, $J=7.6$ Hz, 3H), 0.78 (br d, $J=5.5$ Hz, 3H), 0.59 - 0.54 (m, 3H) hLPA1 $\text{IC}_{50} = 27$ nM	
198	 (1S,3S)-3-(((6-(5-(((benzylcarbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 494.0$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.3$ Hz, 2H), 7.47 (br d, $J=8.5$ Hz, 1H), 7.32 - 7.27 (m, 2H), 7.22 (br d, $J=7.2$ Hz, 3H), 5.69 (s, 2H), 4.76 (br s, 1H), 4.18 (br d, $J=5.9$ Hz, 2H), 4.08 (s, 3H), 3.50 (br s, 1H), 2.78 (q, $J=7.3$ Hz, 2H), 1.98 (br d, $J=13.0$ Hz, 1H), 1.80 (br d, $J=11.8$ Hz, 3H), 1.61 (br s, 2H), 1.54 (br s, 1H), 1.50 (br s, 1H), 1.22 (br t, $J=7.4$ Hz, 3H) hLPA1 $\text{IC}_{50} = 46$ nM	

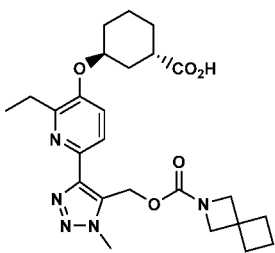
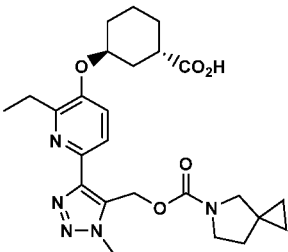
Example	Structure & Name	Analytical & Biology Data	Method
199	 (1S,3S)-3-(((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 474.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.3$ Hz, 1H), 7.46 (br d, $J=8.3$ Hz, 1H), 5.64 (br d, $J=12.4$ Hz, 2H), 4.76 (br s, 1H), 4.09 (br s, 3H), 3.53 (br s, 1H), 3.17 (br s, 1H), 3.03 (br s, 1H), 2.82 - 2.69 (m, 5H), 1.98 (br d, $J=13.8$ Hz, 1H), 1.79 (br d, $J=11.0$ Hz, 3H), 1.60 (br s, 2H), 1.57 - 1.45 (m, 2H), 1.41 (br s, 1H), 1.26 - 1.16 (m, 5H), 1.01 - 0.93 (m, 1H), 0.86 (br s, 1H), 0.61 (br s, 2H) hLPA1 $\text{IC}_{50} = 7$ nM	
200	 (1S,3S)-3-((2-ethyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 460.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.92 - 7.70 (m, 1H), 7.62 - 7.30 (m, 1H), 5.80 - 5.48 (m, 2H), 4.89 - 4.58 (m, 1H), 4.24 - 3.82 (m, 3H), 3.60 - 3.25 (m, 1H), 3.21 - 2.93 (m, 2H), 2.85 - 2.67 (m, 5H), 2.66 - 2.56 (m, 1H), 2.07 - 1.94 (m, 1H), 1.90 - 1.69 (m, 3H), 1.68 - 1.36 (m, 5H), 1.33 - 1.14 (m, 3H), 0.86 - 0.67 (m, 2H), 0.67 - 0.40 (m, 2H) hLPA1 $\text{IC}_{50} = 11$ nM	

Example	Structure & Name	Analytical & Biology Data	Method
201	 (1S,3S)-3-(((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 474.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.3$ Hz, 1H), 7.46 (br d, $J=8.3$ Hz, 1H), 5.64 (br d, $J=12.4$ Hz, 2H), 4.76 (br s, 1H), 4.09 (br s, 3H), 3.53 (br s, 1H), 3.17 (br s, 1H), 3.03 (br s, 1H), 2.82 - 2.69 (m, 5H), 1.98 (br d, $J=13.8$ Hz, 1H), 1.79 (br d, $J=11.0$ Hz, 3H), 1.60 (br s, 2H), 1.57 - 1.45 (m, 2H), 1.41 (br s, 1H), 1.26 - 1.16 (m, 5H), 1.01 - 0.93 (m, 1H), 0.86 (br s, 1H), 0.61 (br s, 2H) hLPA1 $IC_{50} = 25$ nM	
202	 (1S,3S)-3-((2-ethyl-6-(5-(((ethyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 446.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.47 (br d, $J=8.5$ Hz, 1H), 5.66 (br s, 2H), 4.76 (br s, 1H), 4.09 (s, 3H), 3.56 - 3.37 (m, 1H), 3.19 (br d, $J=18.6$ Hz, 1H), 3.11 (br s, 1H), 2.82 - 2.75 (m, 3H), 2.73 (br s, 2H), 2.60 - 2.53 (m, 1H), 1.98 (br d, $J=13.4$ Hz, 1H), 1.80 (br d, $J=11.0$ Hz, 2H), 1.61 (br s, 2H), 1.53 (br d, $J=16.5$ Hz, 2H), 1.24 (t, $J=7.5$ Hz, 3H), 1.00 (br d, $J=6.1$ Hz, 2H), 0.86 (br s, 2H) hLPA1 $IC_{50} = 160$ nM	

Example	Structure & Name	Analytical & Biology Data	Method
203	 (1S,3S)-3-(((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.81 (br d, $J=8.2$ Hz, 1H), 7.46 (br d, $J=8.9$ Hz, 1H), 5.62 (s, 2H), 4.74 (br s, 1H), 4.07 (s, 3H), 3.77 - 3.70 (m, 4H), 2.77 (q, $J=7.3$ Hz, 2H), 2.70 (br s, 2H), 2.03 (br s, 1H), 1.93 (br d, $J=13.1$ Hz, 2H), 1.88 - 1.72 (m, 5H), 1.63 - 1.41 (m, 6H), 1.21 (br t, $J=7.3$ Hz, 3H) hLPA1 $\text{IC}_{50} = 8$ nM	
204	 (1S,3S)-3-(((6-(5-(((3,3-dimethylazetidine-1-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 472.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.81 (br d, $J=8.5$ Hz, 1H), 7.46 (br d, $J=8.5$ Hz, 1H), 5.62 (s, 2H), 4.74 (br s, 1H), 4.05 (s, 3H), 3.79 - 3.70 (m, 4H), 2.78 (q, $J=7.3$ Hz, 2H), 1.91 (br s, 1H), 1.86 - 1.73 (m, 5H), 1.64 - 1.44 (m, 4H), 1.22 (t, $J=7.5$ Hz, 3H), 1.13 (s, 6H) hLPA1 $\text{IC}_{50} = 102$ nM	
205	 (1S,3S)-3-(((6-(5-(((bicyclo[1.1.1]pentan-1-ylcarbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 470.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.82 (br d, $J=7.3$ Hz, 1H), 7.48 (br s, 1H), 5.62 (br s, 2H), 4.99 - 4.53 (m, 1H), 4.07 (br s, 2H), 3.58 (br s, 1H), 3.17 (s, 1H), 2.89 (s, 1H), 2.82 (br s, 1H), 2.73 (s, 1H), 2.35 (br s, 1H), 2.05 (br s, 1H), 1.90 (br s, 7H), 1.64 (br s, 4H), 1.25 (br s, 3H), 1.00 (d, $J=6.1$ Hz, 1H) hLPA1 $\text{IC}_{50} = 842$ nM	

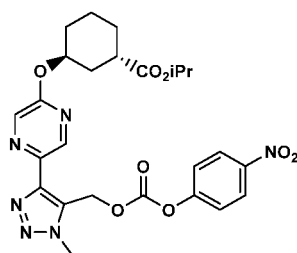
Example	Structure & Name	Analytical & Biology Data	Method
206	 (1S,3S)-3-(((6-(5-(((bicyclo[1.1.1]pentan-1-yl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484.1$ 1H NMR (500 MHz, DMSO-d_6) δ 7.88 - 7.75 (m, $J=8.2$ Hz, 1H), 7.54 - 7.41 (m, $J=8.2$ Hz, 1H), 5.63 (s, 2H), 4.88 - 4.67 (m, 1H), 4.09 (s, 2H), 3.69 - 3.53 (m, 1H), 3.17 (s, 1H), 2.89 (s, 1H), 2.80 (br d, $J=7.3$ Hz, 2H), 2.76 - 2.63 (m, 3H), 2.05 (br s, 1H), 1.79 (br s, 8H), 1.61 (br s, 4H), 1.22 (br t, $J=7.3$ Hz, 3H), 1.00 (d, $J=6.4$ Hz, 1H) hLPA1 $IC_{50} = 34$ nM	
207	 (1S,3S)-3-(((2-ethyl-6-(1-methyl-5-(((methyl(1-propylcyclopropyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 500.4$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.47 (br d, $J=8.5$ Hz, 1H), 5.64 (br d, $J=8.5$ Hz, 2H), 4.78 (br s, 1H), 4.12 (s, 2H), 4.08 (br s, 1H), 2.83 - 2.73 (m, 4H), 2.73 - 2.65 (m, 1H), 2.60 (br s, 1H), 2.12 - 1.94 (m, 1H), 1.86 (br d, $J=12.2$ Hz, 1H), 1.82 - 1.70 (m, 2H), 1.66 - 1.52 (m, 3H), 1.52 - 1.37 (m, 2H), 1.31 - 1.22 (m, 4H), 1.20 (br s, 1H), 1.06 (br d, $J=8.2$ Hz, 1H), 1.00 (d, $J=6.1$ Hz, 1H), 0.84 (br s, 1H), 0.74 (br s, 1H), 0.68 - 0.54 (m, 4H), 0.44 (br s, 1H) hLPA1 $IC_{50} = 133$ nM	

Example	Structure & Name	Analytical & Biology Data	Method
208	 (1S,3S)-3-((2-ethyl-6-(((((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 488.3$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.89 - 7.77 (m, $J=8.5$ Hz, 1H), 7.53 - 7.41 (m, $J=8.5$ Hz, 1H), 5.64 (br s, 2H), 4.76 (br s, 1H), 4.09 (s, 3H), 3.27 - 3.10 (m, 1H), 3.04 (br s, 1H), 2.89 (s, 1H), 2.82 - 2.67 (m, 5H), 1.98 (br d, $J=12.8$ Hz, 1H), 1.89 (s, 3H), 1.80 (br d, $J=11.6$ Hz, 2H), 1.61 (br d, $J=8.5$ Hz, 2H), 1.54 (br s, 1H), 1.49 (br d, $J=11.3$ Hz, 1H), 1.30 (br d, $J=5.8$ Hz, 1H), 1.24 (br t, $J=7.5$ Hz, 3H), 1.12 (br s, 1H), 0.86 (br s, 3H), 0.60 (br s, 3H) hLPA1 $\text{IC}_{50} = 26$ nM	
209	 (1S,3S)-3-(((6-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 486.4$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=7.6$ Hz, 1H), 7.46 (br d, $J=8.5$ Hz, 1H), 5.65 (br d, $J=10.7$ Hz, 2H), 4.77 (br s, 1H), 4.09 (br s, 3H), 3.24 (br s, 1H), 3.12 (br s, 1H), 2.95 - 2.85 (m, 1H), 2.83 - 2.71 (m, 5H), 2.61 (br t, $J=10.5$ Hz, 1H), 2.08 - 1.95 (m, 1H), 1.92 - 1.82 (m, 2H), 1.82 - 1.73 (m, 2H), 1.66 - 1.45 (m, 4H), 1.33 (br s, 1H), 1.28 - 1.11 (m, 4H), 0.35 (br s, 1H), 0.16 (br s, 1H), -0.01 (br s, 1H), -0.27 (br s, 1H) hLPA1 $\text{IC}_{50} = 22$ nM	

Example	Structure & Name	Analytical & Biology Data	Method
210	 (1S,3S)-3-((6-(5-(((2-azaspiro[3.3]heptane-2-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484.4$ 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.5$ Hz, 1H), 7.46 (d, $J=8.5$ Hz, 1H), 5.64 (s, 2H), 4.77 (br s, 1H), 4.07 (s, 3H), 2.93 - 2.86 (m, 1H), 2.80 (q, $J=7.3$ Hz, 2H), 2.73 (s, 1H), 2.61 (br t, $J=10.7$ Hz, 1H), 2.09 - 1.99 (m, 5H), 1.93 - 1.82 (m, 3H), 1.82 - 1.67 (m, 4H), 1.65 - 1.52 (m, 3H), 1.50 (br s, 1H), 1.28 - 1.14 (m, 3H) hLPA1 $IC_{50} = 67$ nM	
211	 (1S,3S)-3-((6-(5-(((5-azaspiro[2.4]heptane-5-carbonyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-ethylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 484.4$ 1H NMR (500 MHz, DMSO-d_6) δ 7.87 - 7.80 (m, 1H), 7.46 (br d, $J=8.9$ Hz, 1H), 5.69 (br d, $J=5.8$ Hz, 2H), 4.77 (br s, 1H), 4.09 (br d, $J=15.3$ Hz, 3H), 3.15 (s, 1H), 3.07 (s, 1H), 2.89 (s, 1H), 2.80 (q, $J=7.6$ Hz, 2H), 2.73 (s, 1H), 2.61 (br t, $J=10.5$ Hz, 1H), 2.16 - 1.96 (m, 1H), 1.91 - 1.74 (m, 3H), 1.70 (t, $J=6.9$ Hz, 2H), 1.65 - 1.45 (m, 4H), 1.29 - 1.14 (m, 3H), 0.55 (br s, 1H), 0.53 - 0.45 (m, 3H) hLPA1 $IC_{50} = 47$ nM	

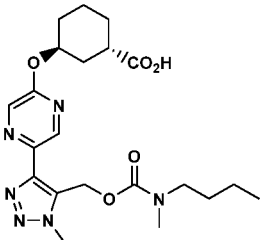
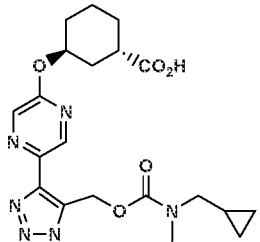
The following analogs were synthesized according to the methods described for the preparation of Example 1 except that the intermediate 4 was used (instead of Example 1F).

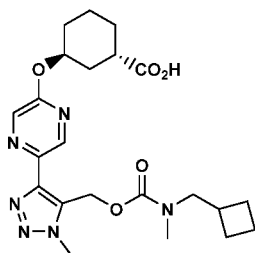
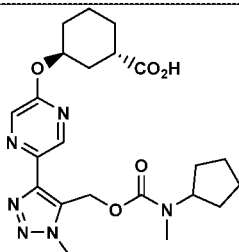
5



Intermediate 4

Intermediate 3 was prepared from 2,5-dibromo-pyrazine using the same synthetic sequence as described for the preparation of Example 1.

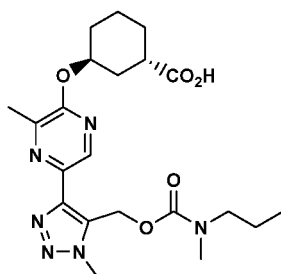
Example	Structure & Name	Analytical & Biology Data	Method
212	 (1S,3S)-3-((5-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, [M+H]⁺ = 447.1 ¹H NMR (500 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.34 (s, 1H), 5.53 (br d, J=15.0 Hz, 2H), 5.36 (br s, 1H), 4.12 (s, 3H), 3.16 (br s, 1H), 3.06 (br s, 1H), 2.74 (br d, J=11.6 Hz, 3H), 2.66 (br t, J=10.1 Hz, 1H), 2.07 (br d, J=13.1 Hz, 1H), 1.87 - 1.79 (m, 3H), 1.66 (br t, J=13.0 Hz, 2H), 1.60 - 1.48 (m, 2H), 1.41 (br s, 1H), 1.22 (br s, 2H), 1.06 - 0.99 (m, 1H), 0.86 (br s, 1H), 0.68 (br s, 2H) hLPA1 IC₅₀ = 40 nM	Example 1
213	 (1S,3S)-3-((5-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, [M+H]⁺ = 445.1 ¹H NMR (500 MHz, DMSO-d₆) δ 8.80 - 8.73 (m, 1H), 8.37 - 8.30 (m, 1H), 5.54 (br d, J=13.1 Hz, 2H), 5.40 - 5.31 (m, 1H), 4.12 (s, 3H), 3.12 - 3.02 (m, 1H), 3.02 - 2.92 (m, 1H), 2.83 (br s, 3H), 2.70 - 2.60 (m, 1H), 2.12 - 2.01 (m, 1H), 1.86 - 1.79 (m, 3H), 1.71 - 1.61 (m, 2H), 1.59 - 1.48 (m, 2H), 0.98 - 0.85 (m, 1H), 0.85 - 0.70 (m, 1H), 0.49 - 0.36 (m, 1H), 0.36 - 0.23 (m, 1H), 0.23 - 0.09 (m, 1H), 0.09 - -0.07 (m, 1H) hLPA1 IC₅₀ = 1070 nM	Example 1

Example	Structure & Name	Analytical & Biology Data	Method
214	 (1S,3S)-3-((5-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, [M+H]⁺ = 459.0 ¹H NMR (500 MHz, DMSO-d₆) δ 8.75 (s, 1H), 8.33 (br s, 1H), 5.51 (br d, J=16.5 Hz, 2H), 5.34 (br s, 1H), 4.12 (br s, 3H), 3.56 (br s, 1H), 3.18 (br d, J=10.4 Hz, 1H), 3.08 (br d, J=5.5 Hz, 1H), 2.71 (br d, J=9.5 Hz, 3H), 2.64 (br s, 1H), 2.34 - 2.19 (m, 1H), 2.08 - 2.02 (m, 1H), 1.90 (br s, 1H), 1.86 - 1.78 (m, 3H), 1.75 (br s, 1H), 1.71 (br s, 1H), 1.64 (br d, J=13.4 Hz, 3H), 1.59 - 1.46 (m, 3H), 1.40 (br s, 1H) hLPA1 IC₅₀ = 68 nM	Example 1
215	 (1S,3S)-3-((5-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, [M+H]⁺ = 459.3 ¹H NMR (500 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.34 (s, 1H), 5.54 (s, 2H), 5.35 (br s, 1H), 4.47 - 4.22 (m, 1H), 4.11 (s, 3H), 3.53 - 3.31 (m, 1H), 2.63 (br s, 4H), 2.10 - 2.03 (m, 1H), 1.87 - 1.76 (m, 3H), 1.73 - 1.60 (m, 3H), 1.57 (br s, 3H), 1.51 (br d, J=12.2 Hz, 2H), 1.43 (br s, 4H) hLPA1 IC₅₀ = 84 nM	Example 1

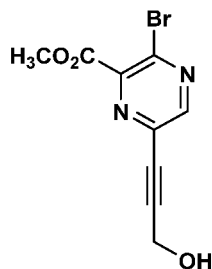
Example 216

(1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-

5 triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid



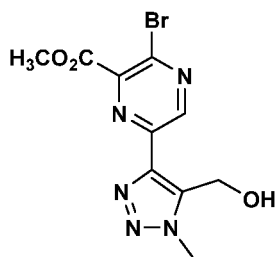
216A. Methyl 3-bromo-6-(3-hydroxyprop-1-yn-1-yl)pyrazine-2-carboxylate



5 A mixture of methyl 3,6-dibromopyrazine-2-carboxylate (16.5 g, 55.8 mmol), propargyl alcohol (3.33 mL, 55.8 mmol), and TEA (46.6 mL, 335 mmol) in MeCN (100 mL) was degassed with N₂ and then CuI (0.531 g, 2.79 mmol) and bis(triphenylphosphine)Palladium(II) chloride (1.96 g, 2.79 mmol) were successively added. The reaction mixture was degassed with N₂ for 3 cycles & stirred at rt for 18 h,
 10 then was filtered through a pad of Celite. The filtrate was concentrated in vacuo. The crude oil was chromatographed (120 g SiO₂ eluted with EtOAc/hexane using a continuous gradient from 0% to 80% over 25 min) to give the title product (5.40 g, 19.9 mmol, 35.7 % yield) as a brownish oil.

¹H NMR (500 MHz, CDCl₃) δ 8.53 (s, 1H), 4.56 (d, *J*=6.3 Hz, 2H), 4.04 (s, 3H), 2.09 -
 15 2.00 (m, 1H)

216B. Methyl 3-bromo-6-(5-(hydroxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate



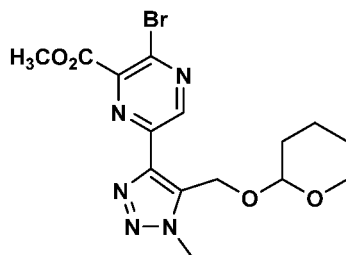
20

To a solution of Example 216A (2.7 g, 9.96 mmol) in 1,4-dioxane (100 mL) were successively added TMSCH₂N₃ (1.48 mL, 9.96 mmol), chloro(pentamethylcyclopenta-dienyl)bis(triphenylphosphine)Ruthenium(II) (0.397 g, 0.498 mmol), and CuI (0.095 g, 0.498 mmol). The mixture was degassed with N₂ for 3
 25 cycles. The resulting homogenous mixture was then heated at 50°C (oil bath) for 16h,

then was cooled to rt and concentrated *in vacuo*. The residue was dissolved in THF (40 mL) and cooled to 0 °C; TBAF (19.9 mL of a 1 M solution in THF, 19.9 mmol) was added at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 60 min, after which sat. aq. NaHCO₃ aqueous solution (20 mL) was added. The mixture was stirred for 1 h and filtered. The filtrate was concentrated *in vacuo*. The crude brown oily product was chromatographed (SiO₂; 80 g; elution with EtOAc/Hexane - continuous gradient from 0% to 80% over 25 min) to give title product (1.5 g, 4.57 mmol, 45.9 % yield) as a light brownish solid.

¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 4.90 - 4.85 (m, 3H), 4.15 (s, 3H), 4.07 (s, 3H)

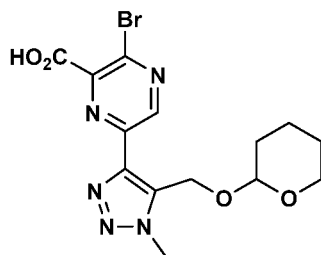
216C. Methyl 3-bromo-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate



p-TsOH.H₂O (0.087 g, 0.457 mmol) was added to a solution of Example 216B (3.0 g, 9.14 mmol) and 3,4-dihydro-2H-pyran (2.502 mL, 27.4 mmol) in DCM (10 mL) at 0°C. The reaction mixture was stirred overnight at rt and neutralized with satd aq. NaHCO₃ to pH 7 at 0°C. The mixture was partitioned between CH₂Cl₂ (10 mL) and water (10 mL), and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated in vacuo. The crude oil was chromatographed (40 g SiO₂; elution with EtOAc/Hexane - continuous gradient from 0% to 50% over 25 min) to give the title compound (3.50 g, 8.49 mmol, 93 % yield) as light brownish oil.

[M - THP + H]⁺ = 328.1/330.1; ¹H NMR (400 MHz, CDCl₃) δ 9.31 (s, 1H), 5.28 - 5.09 (m, 2H), 4.75 - 4.71 (m, 1H), 4.19 (s, 3H), 4.03 (s, 3H), 3.82 - 3.75 (m, 1H), 3.53 - 3.45 (m, 1H), 1.85 - 1.44 (m, 6H)

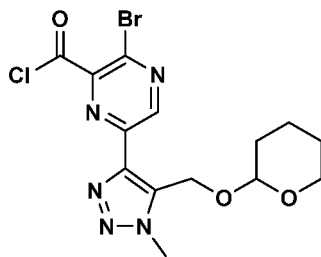
216D. 3-Bromo-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazine-2-carboxylic acid



- 5 A solution of LiOH.H₂O (0.484 g, 11.53 mmol) in water (6 mL) was added dropwise to a stirred solution of Example 216C (1.0 g, 2.43 mmol) in THF (6 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 60 min, then was quenched carefully with 1N aq. HCl to pH ~5 at 0 °C and extracted with DCM (20 × 5 mL). The combined organic extracts were washed with brine and dried over Na₂SO₄.
- 10 Volatiles were removed in vacuo to afford the title compound (0.80 g, 2.01 mmol, 83 % yield) as a light yellowish solid.
- [M – THP + H]⁺ = 313.9/315.9; ¹H NMR (500 MHz, CDCl₃) δ 9.46 (s, 1H), 5.42 (d, J=13.5 Hz, 1H), 4.90 (d, J=13.8 Hz, 1H), 4.24 (s, 3H), 3.87 (td, J=10.9, 2.6 Hz, 1H), 3.73 (d, J=11.3 Hz, 1H), 1.93 - 1.50 (m, 7H)

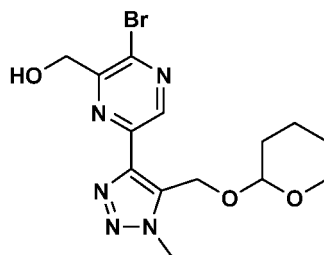
15

217E. 3-Bromo-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazine-2-carbonyl chloride



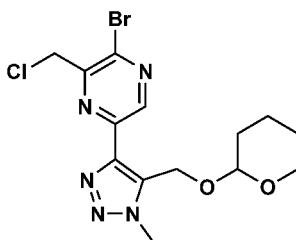
- A mixture of Example 217D (228 mg, 0.573 mmol) and 1-chloro-N,N,2-trimethylprop-1-en-1-amine (0.114 mL, 0.859 mmol) in DCM (2 mL) was stirred at rt for 1 h. The reaction mixture was concentrated in vacuo to give the title compound (239 mg, 0.574 mmol, 100 % yield) as yellowish oil which was used in the next reaction without further purification.
- 20

218F. (3-Bromo-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)methanol



- A solution of Example 218E (3.14 g, 7.54 mmol) in THF (20 mL) was added dropwise to a suspension of NaBH₄ (0.656 g, 17.33 mmol) in EtOH (20 mL) at -78 °C. The reaction was stirred at -78 °C for 1 h. Aq. HCl (9.80 mL of a 1.0 N solution, 9.80 mmol) was added cautiously to the reaction to make it weakly acidic at -78 °C. The mixture was then basified with sat'd aq. NaHCO₃ to pH ~ 8 and extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The crude oily product was chromatographed (40 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 80% over 25 min) to give the title compound (2.50 g, 6.51 mmol, 86 % yield) as a light yellowish solid.
- ¹H NMR (500 MHz, CDCl₃) δ 9.13 (s, 1H), 5.47 (d, *J*=13.2 Hz, 1H), 4.98 (d, *J*=13.2 Hz, 1H), 4.89 - 4.85 (m, 2H), 4.76 (t, *J*=2.9 Hz, 1H), 4.69 (t, *J*=5.6 Hz, 1H), 4.19 (s, 3H), 3.93 - 3.81 (m, 1H), 3.62 (dt, *J*=10.9, 3.9 Hz, 1H), 1.86 - 1.47 (m, 6H)

218G. 2-Bromo-3-(chloromethyl)-5-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazine

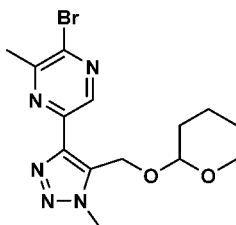


- To a solution of Example 218F (190 mg, 0.494 mmol) in CHCl₃ (3 mL) was added methanesulfonyl chloride (0.057 mL, 0.74 mmol), iPr₂NEt (0.259 mL, 1.48 mmol) and DMAP (6.0 mg, 0.049 mmol) at 0 °C. After the addition was complete, the reaction mixture was stirred at rt for 30 min. after which LiCl (105 mg, 2.472 mmol) and DMF (3 mL) were successively added. The mixture was stirred at rt for 1 h and then concentrated

in vacuo. The residue was partitioned between water and EtOAc (10 mL each). The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude oily product was chromatographed (12 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 50% over 10 min) to give the title compound (175 mg, 0.435 mmol, 88 % yield) as a white solid.

¹H NMR (400MHz, CDCl₃) δ 9.14 (s, 1H), 5.33 - 5.19 (m, 2H), 4.84 (s, 2H), 4.75 (t, *J*=3.4 Hz, 1H), 4.19 (s, 3H), 3.88 - 3.75 (m, 1H), 3.59 - 3.47 (m, 1H), 1.87 - 1.46 (m, 6H)

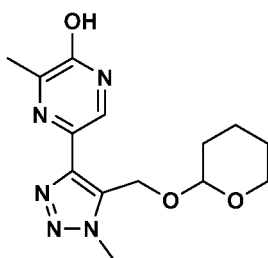
218H. 2-Bromo-3-methyl-5-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazine



To a 0 °C solution of NaBH₄ (286 mg, 7.55 mmol) in EtOH (20 mL) was added dropwise a solution of Example 218G (760 mg, 1.89 mmol) in THF (20 mL). After the addition was complete, the reaction was stirred at rt for 6 h. LCMS indicated the reaction was still not complete, so additional NaBH₄ (286 mg, 7.55 mmol) was added and the reaction mixture was stirred for 3 days, then cautiously quenched with water at 0 °C. The mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The crude oily product was chromatographed (24 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 50% over 10 min) to give the title compound (600 mg, 1.63 mmol, 86 % yield) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 9.04 (s, 1H), 5.29 - 5.20 (m, 2H), 4.75 (t, *J*=3.4 Hz, 1H), 4.20 (s, 3H), 3.86 (ddd, *J*=11.3, 8.3, 3.0 Hz, 1H), 3.59 - 3.50 (m, 1H), 2.72 (s, 3H), 1.85 - 1.49 (m, 6H)

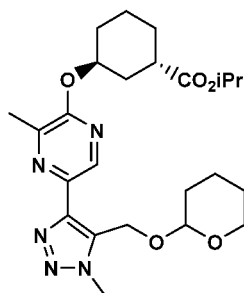
218I. 3-Methyl-5-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-ol



A mixture of Example 218H (600 mg, 1.63 mmol), KOH (1.00 mL of a 7 M aq. solution, 7.0 mmol) in water (5 mL) and dioxane (5 mL) was degassed under N₂ and then tBuXphos (83 mg, 0.196 mmol) and Pd₂(dba)₃ (44.8 mg, 0.049 mmol) were added. The reaction mixture was degassed under N₂ again and then stirred at 80 °C overnight. The reaction was cooled to rt, then was acidified to pH 5 with 1N aq. HCl at 0 °C and partitioned between water and EtOAc. The organic phase was separated, dried (MgSO₄), and concentrated in vacuo. The crude oily product was chromatographed (12 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 100% over 7 min) to give the title compound (340 mg, 1.11 mmol, 68.3 % yield) as a light yellowish solid.

[M – THP + H]⁺ = 222.2; ¹H NMR (500 MHz, CDCl₃) δ 8.04 (s, 1H), 5.24 - 5.15 (m, 2H), 4.88 - 4.72 (m, 1H), 4.16 (s, 3H), 3.90 (ddd, *J*=11.2, 8.2, 3.2 Hz, 1H), 3.72 - 3.52 (m, 1H), 2.55 (s, 3H), 1.90 - 1.44 (m, 7H)

218J. Isopropyl (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylate

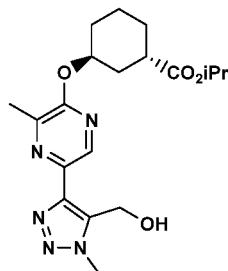


To a mixture of Example 218I (340 mg, 1.11 mmol), ((1S,3R)-isopropyl 3-hydroxycyclo-hexane carboxylate (373 mg, 2.00 mmol) in THF (5 mL) were successively added n-Bu₃P (0.556 mL, 2.227 mmol) and (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (562 mg, 2.23 mmol). The reaction mixture was then stirred at 80 °C for 18 h, then was cooled to rt and concentrated in vacuo. The crude oily product was chromatographed (24 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0%

to 50% over 10 min) to give the title compound (527 mg, 1.11 mmol, 100 % yield) as a clear oil.

$[M + H]^+ = 474.2$

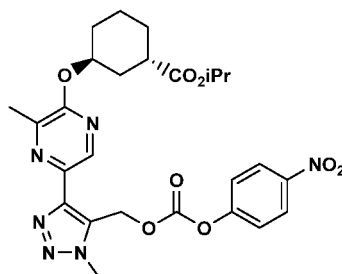
- 5 218K. Isopropyl (1S,3S)-3-((5-(5-(hydroxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylate



- A mixture of Example 218J (527 mg, 1.11 mmol) and pyridinium p-toluenesulfonate (28 mg, 0.11 mmol) in MeOH (10 mL) was stirred at rt for 3 days and
 10 then concentrated in vacuo. The crude oily product was chromatographed (24 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 100% over 10 min) to give the title compound (277 mg, 0.711 mmol, 63.9 % yield) as a clear oil.

- $[M + H]^+ = 390.2$; ¹H NMR (500 MHz, CDCl₃) δ 8.89 (s, 1H), 5.54 (br s, 1H), 5.04 (dt, *J*=12.4, 6.3 Hz, 1H), 4.83 (s, 2H), 4.16 - 4.10 (m, 3H), 2.74 (tt, *J*=11.1, 3.9 Hz, 1H), 2.56
 15 (s, 3H), 2.23 (br d, *J*=14.0 Hz, 1H), 2.01 (br dd, *J*=8.8, 4.1 Hz, 2H), 1.89 (ddd, *J*=13.9, 11.4, 2.8 Hz, 1H), 1.82 - 1.47 (m, 5H), 1.26 (dd, *J*=6.3, 2.8 Hz, 6H)

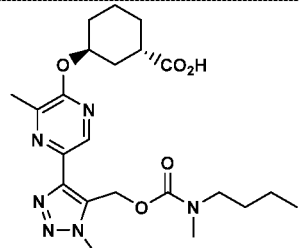
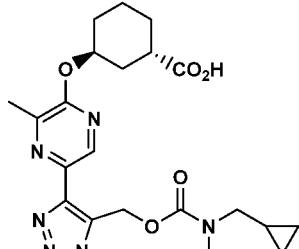
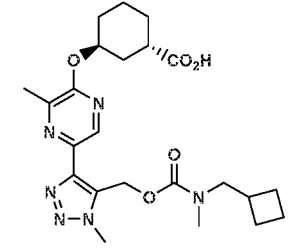
- 218L. Isopropyl (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((4-nitrophenoxy)carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-
 20 1-carboxylate

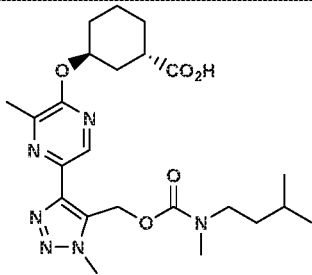
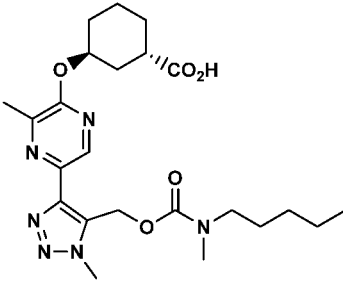
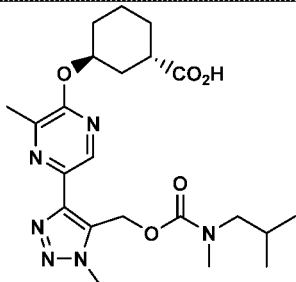


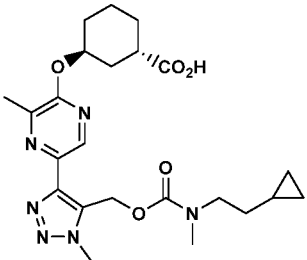
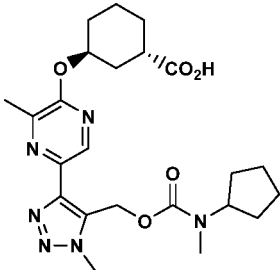
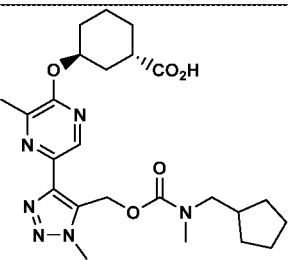
A solution of 4-nitrophenyl chloroformate (172 mg, 0.854 mmol) in DCM (1 mL) was added dropwise to a solution of Example 218K (277 mg, 0.711 mmol) and pyridine (0.288 mL, 3.56 mmol) in DCM (5 mL) over 1 h at 0°C. The reaction was then stirred at rt for 18 h, then was concentrated in vacuo. The crude oily product was chromatographed (12 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 50% over 10 min) to give the title compound (366 mg, 0.66 mmol, 93 % yield) as a light yellowish oil. [M + H]⁺ = 555.2; ¹H NMR (500 MHz, CDCl₃) δ 8.79 (s, 1H), 8.33 - 8.28 (m, 2H), 7.44 - 7.37 (m, 2H), 6.02 - 5.94 (m, 2H), 5.52 (br s, 1H), 5.03 (dt, *J*=12.6, 6.2 Hz, 1H), 4.23 (s, 3H), 2.74 (tt, *J*=11.1, 3.9 Hz, 1H), 2.52 (s, 3H), 2.22 (br d, *J*=14.0 Hz, 1H), 2.03 - 1.96 (m, 2H), 1.93 - 1.83 (m, 1H), 1.81 - 1.52 (m, 4H), 1.30 - 1.22 (m, 6H)

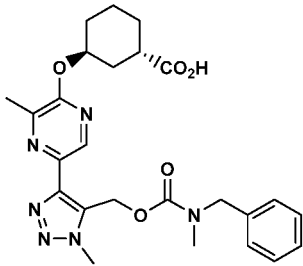
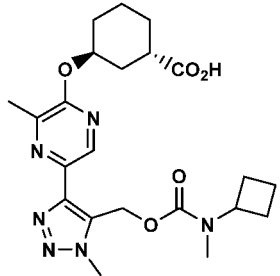
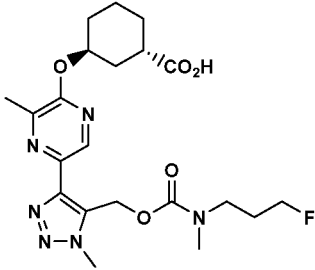
Example 218.

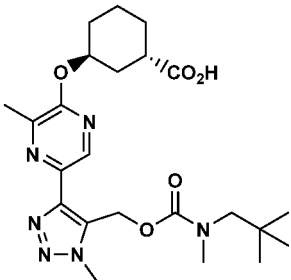
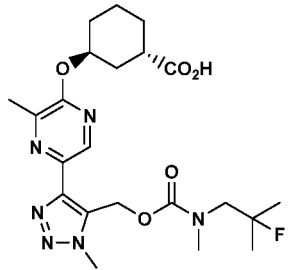
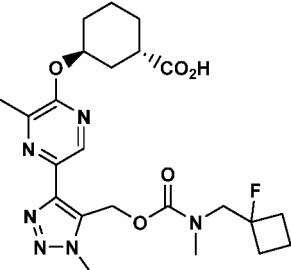
To a solution of Example 218L (8 mg, 0.014 mmol) in DCM (1 mL) was added *N*-methyl propan-1-amine (1.8 μL; 0.017 mmol) and DIPEA (7.6 μL, 0.043 mmol). The reaction mixture was stirred at rt for 2 h, then was concentrated in vacuo. The crude oil was (4 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 30% over 10 min) to give the corresponding carbamate-isopropyl ester Example as a clear oil. This ester intermediate was stirred with 1N aq. NaOH (0.2 mL) in THF (1 mL) and MeOH (0.2 mL) at rt for 18 h and then acidified to pH = ~2 with TFA. The reaction mixture was purified by preparative HPLC (Sunfire C18 30 x 100 mm-regenerated 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:MeCN:TFA and B = 90:10:0.1 MeCN:H₂O:TFA) to give Example 218 (5 mg, 11.0 μmol, 76 % yield) as a clear oil. [M + H]⁺ = 447.3; ¹H NMR (500 MHz, CDCl₃) δ 8.72 (s, 1H), 5.69 (br d, *J*=7.4 Hz, 2H), 5.53 (br s, 1H), 4.18 (s, 3H), 3.26 (br t, *J*=7.2 Hz, 1H), 3.13 (br t, *J*=7.2 Hz, 1H), 2.97 - 2.79 (m, 4H), 2.52 (s, 3H), 2.32 (br d, *J*=14.0 Hz, 1H), 2.16 - 1.99 (m, 2H), 1.93 - 1.37 (m, 7H), 0.98 - 0.71 (m, 3H). hLPA IC₅₀ = 194 nM

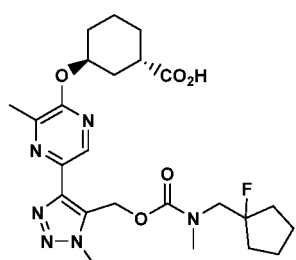
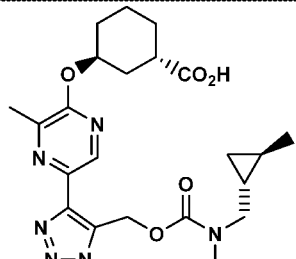
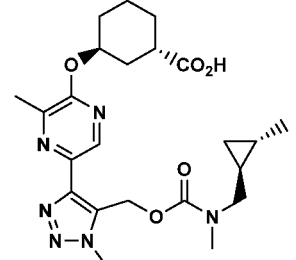
Example	Structure & Name	Analytical & Biology Data	Method
219	 (1S,3S)-3-((5-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 461.4$, ^1H NMR (500 MHz, CDCl_3) δ 8.69 (s, 1H), 5.68 (br. s., 2H), 5.53 (br. s., 1H), 4.19 (s, 3H), 3.36 - 3.10 (m, 2H), 2.97 - 2.79 (m, 4H), 2.53 (s, 3H), 2.32 (d, $J=14.0$ Hz, 1H), 2.14 - 1.97 (m, 2H), 1.94 - 1.12 (m, 9H), 1.02 - 0.74 (m, 3H) hLPA1 $\text{IC}_{50} = 21$ nM	Example 218
220	 (1S,3S)-3-((5-(5-(((cyclopropyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 458.9$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 8.57 (s, 1H), 5.54 (d, $J = 19.1$ Hz, 2H), 5.38 (s, 1H), 4.10 (s, 3H), 3.05 (br s, 1H), 2.93 (br s, 1H), 2.85 - 2.76 (m, 2H), 2.54 (s, 3H), 2.44 (s, 3H), 2.41 - 2.12 (m, 8H), 0.40 (br s, 1H), 0.24 (br s, 1H), 0.16 (br s, 1H), -0.04 (br s, 1H). hLPA1 $\text{IC}_{50} = 149$ nM	Example 218
221	 (1S,3S)-3-((5-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M+H]^+ = 473.2$. ^1H NMR (500 MHz, CDCl_3): δ 8.66 (s, 1H), 5.64 (br s, 2H), 5.51 (s, 1H), 4.17 (s, 3H), 3.31 (d, $J = 7.5$ Hz, 1H), 3.17 (d, $J = 7.3$ Hz, 1H), 2.91 - 2.77 (m, 4H), 2.61 - 2.35 (m, 1H), 2.50 (s, 3H), 2.29 (d, $J = 14.1$ Hz, 1H), 2.10 - 1.50 (m, 13H). hLPA1 $\text{IC}_{50} = 23$ nM	Example 218

Example	Structure & Name	Analytical & Biology Data	Method
222	 (1S,3S)-3-((5-(5-(((isopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 475.4$; ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (br s, 1H), 5.54 (br d, $J=13.0$ Hz, 2H), 5.38 (br s, 1H), 4.12 (br s, 3H), 3.18 (br d, $J=9.2$ Hz, 1H), 3.03 (br s, 1H), 2.80 - 2.58 (m, 4H), 2.44 (br s, 3H), 2.09 (br d, $J=13.6$ Hz, 1H), 1.94 - 1.03 (m, 10H), 0.92 - 0.55 (m, 6H) hLPA1 $\text{IC}_{50} = 19$ nM	Example 218
223	 (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(pentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 475.4$; ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 5.54 (br d, $J=15.9$ Hz, 2H), 5.37 (br s, 1H), 4.11 (br s, 2H), 3.22 - 2.99 (m, 2H), 2.80 - 2.67 (m, 3H), 2.62 - 2.53 (m, 4H), 2.44 (s, 2H), 2.13 - 1.96 (m, 1H), 1.90 - 0.59 (m, 15H) hLPA1 $\text{IC}_{50} = 56$ nM	Example 218
224	 (1S,3S)-3-((5-(5-(((isobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 461.2$; ^1H NMR (500 MHz, CDCl_3): δ 8.72 (s, 1H), 5.69 (br d, $J=14.3$ Hz, 2H), 5.53 (br s, 1H), 4.18 (s, 3H), 3.12 (br d, $J=7.4$ Hz, 1H), 3.03 - 2.77 (m, 6H), 2.53 (s, 3H), 2.32 (br d, $J=14.0$ Hz, 1H), 2.18 - 1.53 (m, 7H), 0.99 - 0.74 (m, 6H) hLPA1 $\text{IC}_{50} = 121$ nM	Example 218

Example	Structure & Name	Analytical & Biology Data	Method
225	 (1S,3S)-3-(((5-(5-(((2-cyclopropylethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 473.4$, 1H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 5.54 (br d, $J=14.4$ Hz, 2H), 5.38 (br s, 1H), 4.11 (br s, 3H), 3.29 - 3.07 (m, 2H), 2.82 - 2.70 (m, 3H), 2.57 (br d, $J=11.3$ Hz, 1H), 2.43 (s, 3H), 2.16 - 1.97 (m, 1H), 1.93 - 1.01 (m, 9H), 0.70 - 0.12 (m, 3H), 0.06 - -0.40 (m, 2H) hLPA1 $IC_{50} = 70$ nM	Example 218
226	 (1S,3S)-3-(((5-(5-(((cyclopentyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 473.5$, 1H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 1H), 5.53 (s, 2H), 5.38 (br s, 1H), 4.10 (s, 3H), 3.64 (br s, 1H), 2.62 (br s, 4H), 2.44 (s, 3H), 2.19 - 2.02 (m, 1H), 1.95 - 1.24 (m, 15H) hLPA1 $IC_{50} = 49$ nM	Example 218
227	 (1S,3S)-3-(((5-(5-(((cyclopentylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 487.5$, 1H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 5.61 - 5.48 (m, 2H), 5.40 (br s, 1H), 4.12 (br s, 3H), 3.20 - 2.91 (m, 2H), 2.84 - 2.69 (m, 3H), 2.64 (br s, 1H), 2.48 - 2.42 (m, 3H), 2.10 (br d, $J=13.1$ Hz, 1H), 1.96 - 1.07 (m, 15H), 0.89 (br s, 1H) hLPA1 $IC_{50} = 18$ nM	Example 218

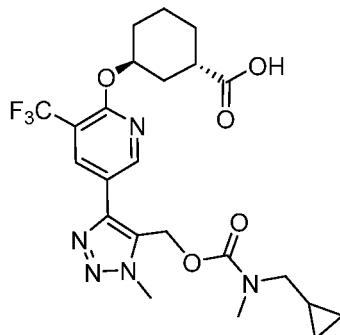
Example	Structure & Name	Analytical & Biology Data	Method
228	 (1S,3S)-3-((5-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 495.3$; ^1H NMR (500 MHz, DMSO-d_6) δ 8.56 (br s, 1H), 7.38 - 7.04 (m, 4H), 6.96 (br s, 1H), 5.68 - 5.47 (m, 2H), 5.37 (br s, 1H), 4.47 - 4.21 (m, 2H), 4.19 - 3.97 (m, 3H), 2.83 - 2.66 (m, 3H), 2.62 (br t, $J=11.0$ Hz, 1H), 2.46 - 2.32 (m, 3H), 2.13 - 2.04 (m, 1H), 1.95 - 1.40 (m, 7H) hLPA1 $\text{IC}_{50} = 60$ nM	
229	 (1S,3S)-3-((5-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 459.0$; ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 - 8.57 (m, 1H), 5.54 (br s, 2H), 5.39 (br s, 1H), 4.10 (s, 4H), 2.82 - 2.57 (m, 4H), 2.47 - 2.39 (m, 3H), 2.18 - 1.31 (m, 14H) hLPA1 $\text{IC}_{50} = 76$ nM	
230	 (1S,3S)-3-((5-(5-(((3-fluoropropyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 465.4$; ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 5.56 (br s, 2H), 5.39 (br s, 1H), 4.54 - 4.17 (m, 2H), 4.11 (s, 3H), 3.39 - 3.14 (m, 2H), 2.89 - 2.69 (m, 3H), 2.64 (br t, $J=10.8$ Hz, 1H), 2.45 (s, 3H), 2.10 (br d, $J=13.7$ Hz, 1H), 1.94 - 1.41 (m, 9H) hLPA1 $\text{IC}_{50} = 390$ nM	

Example	Structure & Name	Analytical & Biology Data	Method
231	 (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl(neopentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 475.2$; ^1H NMR (500 MHz, CHLOROFORM-d) δ 8.71 (s, 1H), 5.68 (br d, $J=12.1$ Hz, 2H), 5.54 (br s, 1H), 4.23 - 4.16 (m, 3H), 3.14 (s, 1H), 3.04 - 2.96 (m, 3H), 2.93 - 2.81 (m, 2H), 2.53 (s, 3H), 2.32 (br d, $J=14.0$ Hz, 1H), 2.16 - 1.97 (m, 2H), 1.94 - 1.84 (m, 1H), 1.83 - 1.55 (m, 4H), 1.04 - 0.72 (m, 9H) hLPA1 $\text{IC}_{50} = 88$ nM	
232	 (1S,3S)-3-((5-(5-(((2-fluoro-2-methylpropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 479.2$; ^1H NMR (500 MHz, CDCl_3): δ 8.67 (s, 1H), 5.80 - 5.57 (m, 2H), 5.54 (br s, 1H), 4.26 - 4.16 (m, 3H), 3.57 - 3.27 (m, 2H), 3.10 - 2.77 (m, 4H), 2.59 - 2.46 (m, 3H), 2.32 (br d, $J=13.8$ Hz, 1H), 2.13 - 1.97 (m, 2H), 1.95 - 1.53 (m, 5H), 1.42 - 1.13 (m, 6H); ^{19}F NMR (471 MHz, CDCl_3): δ -139.12 (s, 1F) hLPA1 $\text{IC}_{50} = 191$ nM	
233	 (1S,3S)-3-((5-(5-(((1-fluorocyclobutyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 491.2$; ^1H NMR (400 MHz, CDCl_3): δ 8.70 (s, 1H), 5.69 (br d, $J=5.1$ Hz, 2H), 5.51 (br s, 1H), 4.16 (s, 3H), 3.72 - 3.34 (m, 2H), 3.04 - 2.75 (m, 4H), 2.49 (br d, $J=4.6$ Hz, 3H), 2.33 - 1.49 (m, 14H); ^{19}F NMR (377 MHz, CDCl_3): δ -130.34 (br s, 1F) hLPA1 $\text{IC}_{50} = 122$ nM	

Example	Structure & Name	Analytical & Biology Data	Method
234	 (1S,3S)-3-((5-(5-((((1-fluorocyclopentyl)methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 505.2$; ^1H NMR (400 MHz, CDCl_3): δ 8.64 (s, 1H), 5.71 - 5.61 (m, 2H), 5.52 (br s, 1H), 4.19 (s, 3H), 3.68 - 3.37 (m, 2H), 3.07 - 2.91 (m, 3H), 2.84 (tt, $J=11.2$, 3.7 Hz, 1H), 2.51 (d, $J=3.5$ Hz, 3H), 2.29 (br d, $J=13.9$ Hz, 1H), 2.12 - 1.96 (m, 2H), 1.94 - 1.35 (m, 13H); ^{19}F NMR (377 MHz, CDCl_3): δ -139.45 to -147.94 (m, 1F) hLPA1 $\text{IC}_{50} = 72$ nM	
235	 (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl((1R,2R)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 473.0$; ^1H NMR (500 MHz, CDCl_3): δ 8.72 (s, 1H), 5.82 - 5.56 (m, 2H), 5.53 (br s, 1H), 4.17 (s, 3H), 3.29 - 2.80 (m, 6H), 2.52 (s, 3H), 2.31 (br d, $J=14.0$ Hz, 1H), 2.14 - 1.97 (m, 2H), 1.91 - 1.54 (m, 5H), 1.10 - 0.90 (m, 3H), 0.75 - 0.11 (m, 4H) hLPA1 $\text{IC}_{50} = 70$ nM	
236	 (1S,3S)-3-((3-methyl-5-(1-methyl-5-(((methyl((1S,2S)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 473.0$; ^1H NMR (500 MHz, CDCl_3): δ 8.72 (s, 5H), 5.69 (br d, $J=6.9$ Hz, 2H), 5.52 (br s, 1H), 4.17 (s, 3H), 3.28 - 2.80 (m, 6H), 2.58 - 2.46 (m, 3H), 2.31 (br d, $J=13.8$ Hz, 1H), 2.12 - 1.97 (m, 2H), 1.93 - 1.54 (m, 5H), 1.10 - 0.89 (m, 3H), 0.74 - 0.11 (m, 4H) hLPA1 $\text{IC}_{50} = 46$ nM	

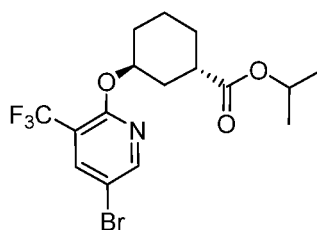
Example 237.

(1S,3S)-3-((5-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid



5

237A. Isopropyl (1S,3S)-3-((5-bromo-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylate



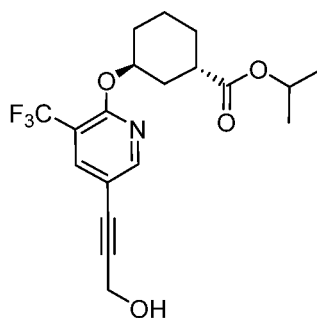
10 To a N₂-flushed, 50 mL round bottom flask was added (E)-diazene-1,2-diylbis (piperidin-1-ylmethanone) (2.11 g, 8.35 mmol), toluene (15 mL) and n-Bu₃P (2.1 mL, 8.35 mmol); the dark orange solution became a light yellow solution after the addition of n-Bu₃P. The solution was stirred at rt for 30 min, then 5-bromo-3-

15 (trifluoromethyl)pyridin-2-ol (1.01 g, 4.17 mmol) and (1S,3R)-isopropyl 3-hydroxycyclohexanecarboxylate (1.40 g, 7.51 mmol) were successively added. The reaction mixture was heated to 80 °C for 16 h, then was cooled to rt. EtOAc (10 mL) and water (5 mL) were added, and the mixture was stirred for 10 min and the organic layer was separated. The aqueous layer was back-extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), and

20 concentrated *in vacuo* to give the crude product. This crude material was chromatographed (SiO₂, 120g; elution with EtOAc/hexanes (continuous gradient from 0 to 100%) to afford the title compound (1.7 g, 4.14 mmol, 99 % yield) as a colorless oil.

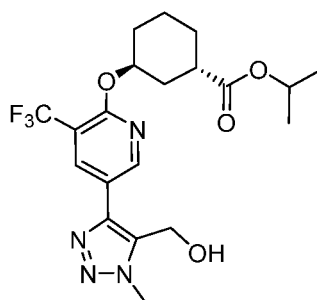
¹H NMR (500 MHz, CDCl₃): δ 8.32 (d, J = 2.4 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H), 5.52 (br s, 1H), 5.06 – 4.94 (m, 1H), 2.69 (tt, J = 11.6, 3.9 Hz, 1H), 2.23 – 2.17 (m, 1H), 2.03 – 1.93 (m, 2H), 1.82 – 1.43 (m, 5H), 1.22 (d, J = 6.3 Hz, 6H). LCMS, [M+H]⁺ = 410.

- 5 237B. Isopropyl (1S,3S)-3-((5-(3-hydroxyprop-1-yn-1-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylate



- To a 100 mL round bottom flask containing Example 237A (1.7 g, 4.1 mmol) and
 10 prop-2-yn-1-ol (0.70 g, 12.4 mmol) in MeCN (21 ml) was added Et₃N (2.89 mL, 20.7 mmol). The solution was quickly degassed (evacuation under vacuum, then refill with N₂ (3x)). Trans-dichlorobis (triphenylphosphine) palladium (II) chloride (0.29 g, 0.41 mmol) and CuI (0.039 g, 0.21 mmol) were added. The solution degassed (evacuation under vacuum, then refill with N₂ (3x)). The reaction was heated to reflux at 80 °C for 24 h,
 15 then was cooled to rt. The reaction mixture was filtered through a Celite® plug, which was washed with EtOAc (2 x 10 mL). The combined filtrates were concentrated *in vacuo* and the residue was chromatographed (40 g SiO₂; continuous gradient from 0% to 100% EtOAc in Hexanes for 20 min) to give the title compound as a white solid (1.13 g, 2.93 mmol, 71 % yield). ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, J = 2.4 Hz, 1H), 7.88 (d, J =
 20 2.5 Hz, 1H), 5.58 (br s, 1H), 5.06 - 4.97 (m, 1H), 4.50 (d, J = 6.2 Hz, 2H), 2.70 (tt, J = 11.6, 3.9 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.03 – 1.93 (m, 2H), 1.82 – 1.43 (m, 5H), 1.22 (d, J = 6.3 Hz, 6H). LCMS, [M+H]⁺ = 386.2.

- 237C. Isopropyl (1S,3S)-3-((5-(5-(hydroxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylate
- 25



To a solution of Example 237B (1.13 g, 2.9 mmol) in 1,4-dioxane (20 mL) was added TMSCH₂N₃ (0.68 g, 5.3 mmol),

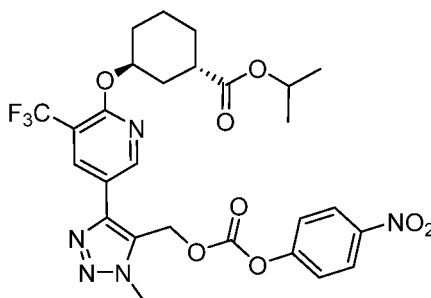
5 chloro(pentamethylcyclopentadienyl)bis(triphenyl- phosphine)Ruthenium(II) (0.12 g, 0.15 mmol), and CuI (0.028 g, 0.15 mmol). The mixture was quickly evacuated and backfilled with N₂ (this sequence was repeated three times). The resulting homogenous mixture was then heated in a 50°C oil bath for 16 h (when the external and internal temp. are between 49 to 50°C), then was cooled to rt and concentrated on a rotary evaporator to

10 dryness (the waste trap content was collected, labeled as azide-containing hazardous waste and disposed accordingly). The residue was dissolved in THF (20 mL). TBAF (5.86 mL of a 1 M solution in THF, 5.86 mmol) was added and the mixture was stirred at rt for 60 min. The reaction was quenched with sat'd aq. NaHCO₃ (20 mL) and extracted with EtOAc (4 x 20 mL). The combined organic extracts were washed with brine (20

15 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude was chromatographed (continuous gradient from 0% to 70% EtOAc/hexanes over 27 min, then gradient from 70 to 100% in 8 min; 80 g Gold ISCO SiO₂ column) and then preparative HPLC under the following conditions: Column: Phenomenex Luna 5u C18 100A 30 x 250 mm; Mobile Phase A: 10:90 MeCN:H₂O with 0.1% TFA; Mobile Phase B: 90:10 MeCN:H₂O

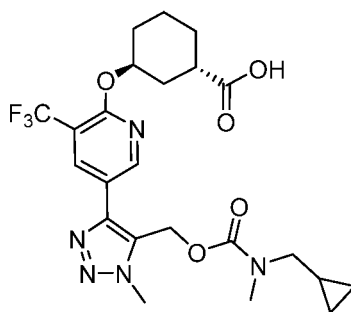
20 with 0.1% TFA; Gradient: 0-100% B over 20 min, then a 5-min hold at 100% B; Flow: 30 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (0.50 g, 1.13 mmol, 38.5 % yield) (the later eluting fraction). ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 2.5 Hz, 1H), 5.62 (br s, 1H), 5.06 – 4.99 (m, 1H), 4.86 (s, 2H), 4.18 (s, 3H), 2.73 (tt, J = 11.5, 3.8 Hz, 1H), 2.28 – 2.22 (m, 1H), 2.05 – 1.98 (m, 2H), 1.85 – 1.45 (m, 5H), 1.22 (d, J = 6.2 Hz, 6H). The regiochemistry of this desired product was determined by 1D-NoE NMR experiments. LCMS, [M+H]⁺ = 443.2.

237D. Isopropyl (1S,3S)-3-((5-(1-methyl-5-(((4-nitrophenoxy)carbonyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylate



- 5 To a solution of Example 237C (116 mg, 0.26 mmol) and 4-nitrophenyl chloroformate (106 mg, 0.52 mmol) in DCM (3 mL) was added pyridine (0.085 mL, 1.05 mmol) at rt. A white solid was formed. The reaction mixture was stirred at rt for 16 h, after which the solid was filtered off and washed with DCM. The combined filtrate and washes were evaporated *in vacuo*. The crude product was chromatographed (12 g SiO₂,
10 elution with continuous gradient from 0 to 100% EtOAc in DCM) to give the title compound (114 mg, 0.19 mmol, 71.6 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.65 (d, J = 2.2 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.31 (d, J = 9.1 Hz, 2H), 7.40 (d, J = 9.1 Hz, 2H), 5.64 (br s, 1H), 5.45 (s, 2H), 5.06 – 4.99 (m, 1H), 4.25 (s, 3H), 2.74 (t, J = 11.7 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.05 – 1.98 (m, 2H), 1.86 – 1.45 (m, 5H), 1.22
15 (d, J = 6.2 Hz, 6H). LCMS, [M+H]⁺ = 608.3.

Example 237

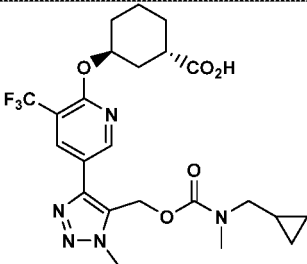
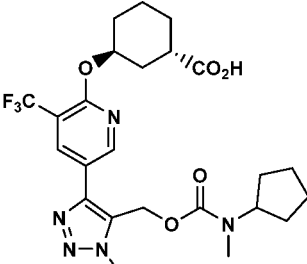


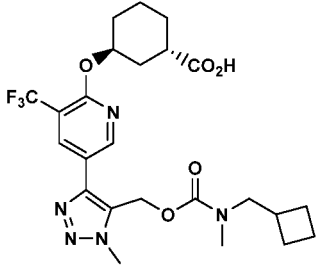
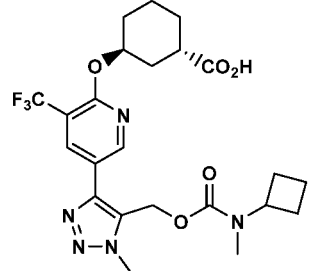
- 20 To a solution of Example 237D (5.4 mg, 8.9 μmol) and 1-cyclopropyl-N-methylmethanamine (2.0 μL, 0.018 mmol) in THF (0.4 mL) was added N-ethyl-N-isopropyl-propan-2-amine (5 μL, 0.027 mmol). The mixture was stirred at rt for 1 h, after which a solution of LiOH·H₂O (3.7 mg, 0.088 mmol) in water (0.4 mL) and MeOH (0.2

mL) was added. The reaction mixture was stirred at rt for 48 h, then was acidified to pH = 4 with 1N aq. HCl and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The crude product was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 MeCN: H₂O with 10 mM NH₄OAc; Mobile Phase B: 95:5 MeCN:H₂O with 10 mM NH₄OAc; Continuous gradient: 20-60% B over 20 min, then a 4-min hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (2.4 mg, 51% yield).

10

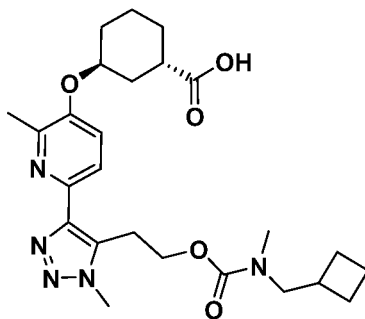
The following compounds were prepared by the general synthetic scheme for Example 237.

Example	Structure & Name	Analytical & Biology Data	Method
237	 (1S,3S)-3-((5-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, [M + H] ⁺ = 512.0. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.75 (s, 1H), 8.32 (s, 1H), 5.55 (br s, 1H), 5.33 (s, 2H), 4.12 (s, 3H), 2.71 (s, 3H), 2.66 – 2.58 (m, 1H), 2.54 (s, 2H), 2.41 – 2.12 (m, 9H), 0.41 (br s, 1H), 0.25 (br s, 1H), 0.18 (br s, 1H), -0.01 (br s, 1H). hLPA1 IC ₅₀ = 2400 nM	Example 237
238	 (1S,3S)-3-((5-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, [M + H] ⁺ = 526.0. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.56 (s, 1H), 8.12 (s, 1H), 5.32 (br s, 1H), 5.15 (s, 1H), 5.11 (s, 1H), 3.91 (s, 3H), 3.0 – 2.85 (m, 3H), 2.50 (s, 3H), 1.88 – 1.13 (m, 15H). hLPA1 IC ₅₀ = 174 nM	

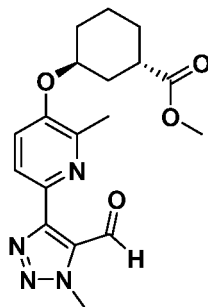
Example	Structure & Name	Analytical & Biology Data	Method
239	 (1S,3S)-3-(((5-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M + H]^+ = 512.5$. 1H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.34 (s, 1H), 5.55 (br s, 1H), 5.33 (s, 2H), 4.12 (s, 3H), 2.71 (s, 3H), 2.54 (s, 2H), 2.12 – 1.36 (m, 14H). hLPA1 $IC_{50} = 440$ nM	
240	 (1S,3S)-3-(((5-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, $[M + H]^+ = 526.0$. 1H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.36 (s, 1H), 5.57 (br s, 1H), 5.37 (br s, 2H), 4.14 (s, 3H), 2.64 (s, 3H), 2.59 – 2.52 (m, 2H), 2.15 – 1.32 (m, 16H). hLPA1 $IC_{50} = 1207$ nM	

Example 241

(1S,3S)-3-(((6-(5-(2-(((Cyclobutylmethyl)(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid

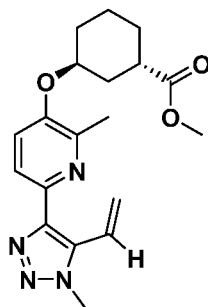


241A. Methyl (1*S*,3*S*)-3-((6-(5-formyl-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylate



To a stirred solution of methyl (1*S*,3*S*)-3-((6-(5-(hydroxymethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylate (3.28 g, 9.10 mmol) in CH₂Cl₂ (45.5 ml) were added NaHCO₃ (3.82 g, 45.5 mmol) and Dess-Martin periodinane (4.63 g, 10.9 mmol) and the reaction mixture was stirred at rt for 1 h. The white solid was filtered off through Celite® and rinsed with EtOAc. The combined filtrates were washed with sat. aq. NaHCO₃, water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was chromatographed (120 g Redisep® SiO₂ column; isocratic 60% EtOAc in Hex) to afford the title compound as a clear, colorless oil (3.10 g, 95 %). LC-MS, [M+H]⁺ = 359.1. ¹H NMR (500 MHz, CDCl₃) δ 10.96 (s, 1H), 8.09 (d, *J*=8.5 Hz, 1H), 7.24 (d, *J*=8.5 Hz, 1H), 4.77 - 4.72 (m, 1H), 4.36 (s, 3H), 3.70 (s, 3H), 2.87 - 2.80 (m, 1H), 2.51 (s, 3H), 2.20 - 2.08 (m, 1H), 2.02 - 1.91 (m, 3H), 1.80 - 1.59 (m, 4H).

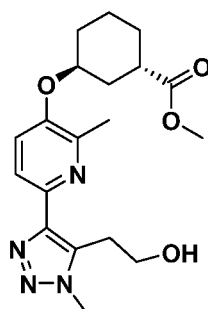
241B Methyl (1*S*,3*S*)-3-((2-methyl-6-(1-methyl-5-vinyl-1*H*-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



To a cooled (0°C) suspension of methyltriphenylphosphonium bromide (3.77 g, 10.55 mmol) in THF (70.3 mL) was added KOtBu (0.947 g, 8.44 mmol), and the reaction

mixture was stirred at 0°C for 30 min. To this reaction mixture was added a solution of Example 241A (2.52 g, 7.03 mmol) in THF (10 mL). The reaction was stirred at 0°C for 30 min, then was allowed to warm to rt. After 1 h at rt, the reaction was quenched with sat. aq. NH₄Cl, then was diluted with EtOAc. The aqueous layer was extracted with EtOAc (2 X 25 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The crude product was chromatographed (220 g Redisep® SiO₂ column; continuous gradient from 0-60% EtOAc in Hex) to afford the title compound as a white gum (2.2 g, 88 %). LC-MS, [M+H]⁺ = 357.0. ¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J*=8.5 Hz, 1H), 7.42 (dd, *J*=18.3, 12.0 Hz, 1H), 7.20 (d, *J*=8.5 Hz, 1H), 5.93 - 5.88 (m, 1H), 5.70 - 5.66 (m, 1H), 4.71 (br s, 1H), 4.15 (s, 3H), 3.70 (s, 3H), 2.84 (tt, *J*=10.5, 3.9 Hz, 1H), 2.53 (s, 3H), 2.16 (br d, *J*=13.8 Hz, 1H), 2.02 - 1.87 (m, 3H), 1.87 - 1.71 (m, 1H), 1.71 - 1.54 (m, 3H).

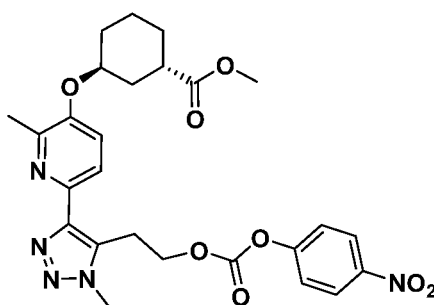
241C Methyl (1*S*,3*S*)-3-((6-(5-(2-hydroxyethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylate



To a cooled (0 °C) solution of Example 241B (1.45 g, 4.07 mmol) in THF (13.6 ml) was added dropwise 9-BBN (17.9 mL of a 0.5M solution in THF; 8.95 mmol). The ice bath was then removed and the reaction was warmed to 65 °C. After 4 h at 65 °C, the reaction mixture was cooled to 0 °C and a solution of sodium perborate tetrahydrate (2.50 g, 16.3 mmol) in water (10 mL) was added. The reaction was then warmed to rt and stirred at rt for 18 h; water was then added. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude product was chromatographed (120 g Redisep® SiO₂ column; continuous gradient from 0-100% EtOAc in Hex) to afford the title compound as a colorless oil (0.37 g, 24 %). LC-MS, [M+H]⁺ = 375.1. ¹H NMR (400 MHz, CDCl₃) δ

7.92 (d, $J=8.6$ Hz, 1H), 7.30 - 7.25 (m, 1H), 6.71 - 6.42 (m, 1H), 4.74 - 4.68 (m, 1H), 4.06 - 3.98 (m, 5H), 3.70 (s, 3H), 3.26 (td, $J=5.6, 1.4$ Hz, 2H), 2.83 (tt, $J=10.3, 3.9$ Hz, 1H), 2.51 (s, 3H), 2.14 (dt, $J=13.9, 4.3$ Hz, 1H), 2.02 - 1.87 (m, 3H), 1.82 - 1.56 (m, 4H).

- 5 241D. Methyl (*1S,3S*)-3-((2-methyl-6-(1-methyl-5-(2-(((4-nitrophenoxy)carbonyl)oxy)ethyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



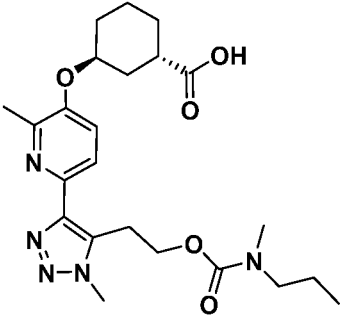
- To a solution of Example 241C (370 mg, 0.988 mmol) and 4-nitrophenyl
 10 chloroformate (299 mg, 1.48 mmol) in THF (9.9 mL) was added pyridine (0.24 mL, 2.96 mmol). The reaction mixture was stirred at rt for 3 h, then was concentrated in vacuo. The crude product was chromatographed (120 g Redisep[®] SiO₂ column; continuous gradient from 0-100% EtOAc in Hex) to afford the title compound as a white solid (387 mg, 72.6 %). LC-MS, $[M+H]^+ = 540.1$. ¹H NMR (500 MHz, CDCl₃) δ 8.30 (d, $J=9.4$
 15 Hz, 2H), 8.03 (d, $J=8.5$ Hz, 1H), 7.34 (d, $J=9.4$ Hz, 2H), 7.24 (d, $J=8.5$ Hz, 1H), 4.75 - 4.69 (m, 3H), 4.14 (s, 3H), 3.72 (s, 3H), 3.66 (t, $J=6.3$ Hz, 2H), 2.89 - 2.83 (m, 1H), 2.50 (s, 3H), 2.17 (br d, $J=14.0$ Hz, 1H), 2.04 - 1.89 (m, 3H), 1.87 - 1.72 (m, 1H), 1.70 - 1.59 (m, 3H).

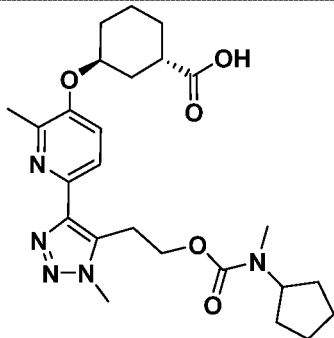
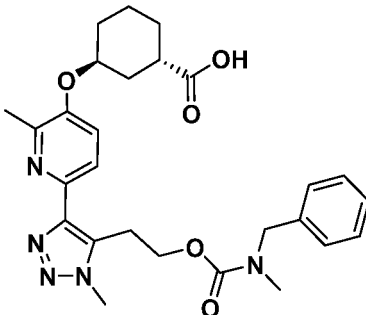
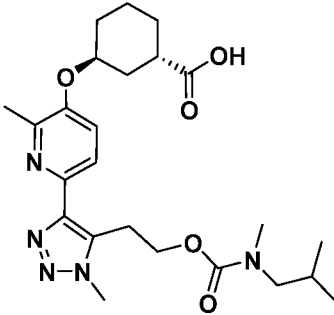
Example 241

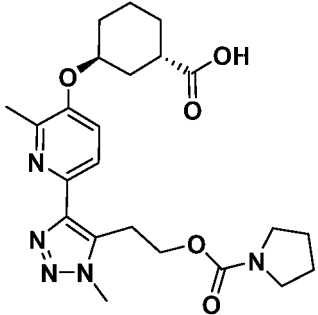
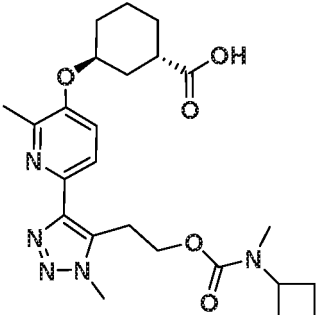
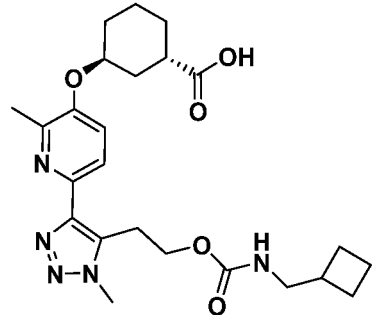
- To a solution of Example 241D (11 mg, 0.020 mmol) and iPr₂NEt (7.1 μ L, 0.041 mmol) in THF (1 mL) was added 1-cyclobutyl-N-methylmethanamine (2.0 mg, 0.020 mmol). The reaction was stirred at rt for 1 h. Water (0.5 mL) was added, followed by aq. LiOH.H₂O (0.05 mL of a 2N solution, 0.10 mmol). The reaction was stirred at rt for 18 h, then was acidified with 1N aq. HCl to pH ~4 and extracted with EtOAc (3 x 5 mL). The
 25 combined organic extracts were washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude material was purified by preparative HPLC (Column: XBridge C18, 19

x 200 mm, 5- μ m particles; Mobile Phase A: 5:95 MeCN: water with 10 mM NH₄OAc; Mobile Phase B: 95:5 MeCN: water with 10 mM NH₄OAc; continuous gradient: 15-55% B over 25 min, then a 4-min hold at 100% B; Flow: 20 mL/min). Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (5.7 mg, 58.7 %). LC-MS, [M+H]⁺ = 486.0. ¹H NMR (500 MHz, DMSO-d₆) δ 7.84 (br s, 1H), 7.48 (br d, *J*=8.5 Hz, 1H), 4.76 (br s, 1H), 4.30 (br s, 2H), 4.02 (s, 3H), 3.53 (br s, 2H), 3.21 - 3.11 (m, 1H), 3.03 - 2.93 (m, 1H), 2.71 (br s, 3H), 2.63 - 2.56 (m, 1H), 2.42 (s, 3H), 2.33 - 2.24 (m, 1H), 2.02 - 1.37 (m, 14H). hLPA1 IC₅₀ = 41 nM.

The following examples were prepared according to the synthetic scheme described for Example 241.

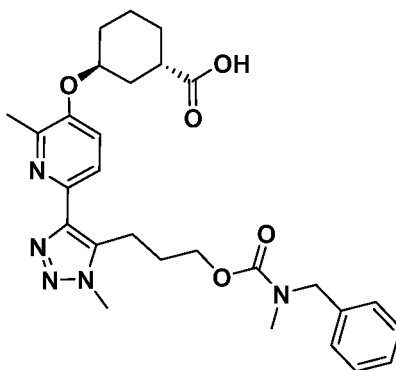
Example	Structure & Name	Analytical & Biology Data	Method
242	 (1<i>S</i>,3<i>S</i>)-3-((2-Methyl-6-(1-methyl-5-(2-((methyl(propyl)carbamoyl)oxy)-ethyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt	LC-MS, [M+H]⁺ = 460.2 ¹H NMR (500 MHz, DMSO-d₆) δ 7.83 (d, <i>J</i>=8.5 Hz, 1H), 7.47 (d, <i>J</i>=8.5 Hz, 1H), 4.78 (br s, 1H), 4.30 (br s, 2H), 4.03 (s, 3H), 3.56- 3.46 (m, 2H), 3.11 - 2.85 (m, 2H), 2.76 - 2.61 (m, 4H), 2.43 (s, 3H), 2.06 - 1.99 (m, 1H), 1.92 - 1.74 (m, 3H), 1.69 - 1.20 (m, 6H), 0.86 - 0.57 (m, 3H). hLPA1 IC₅₀ = 319 nM	Example 241

Example	Structure & Name	Analytical & Biology Data	Method
243	 (1S,3S)-3-((6-(5-(2-((Cyclopentyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC-MS, $[M+H]^+ = 486.0$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.5$ Hz, 1H), 7.46 (br d, $J=8.7$ Hz, 1H), 4.73 (br s, 1H), 4.32 (br t, $J=6.1$ Hz, 2H), 4.23 - 4.11 (m, 1H), 4.01 (s, 3H), 3.53 (br t, $J=6.0$ Hz, 2H), 2.60 - 2.55 (m, 4H), 2.42 (s, 3H), 1.99 - 1.22 (m, 16H). hLPA1 $\text{IC}_{50} = 72$ nM.	Example 241
244	 (1S,3S)-3-((6-(5-(2-((Benzyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC-MS, $[M+H]^+ = 508.0$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.82 (br d, $J=8.2$ Hz, 1H), 7.48 (br d, $J=4.9$ Hz, 1H), 7.36 - 7.24 (m, 3H), 7.15 (br d, $J=5.2$ Hz, 1H), 7.04 (br s, 1H), 4.74 (br s, 1H), 4.43 - 4.30 (m, 3H), 4.17 (br s, 1H), 4.05 - 3.92 (m, 3H), 3.56 - 3.49 (m, 2H), 2.71 (s, 3H), 2.60 - 2.54 (m, 1H), 2.44 - 2.36 (m, 3H), 1.98 - 1.48 (m, 8H). hLPA1 $\text{IC}_{50} = 54$ nM.	Example 241
245	 (1S,3S)-3-((6-(5-(2-((Isobutyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LC-MS, $[M+H]^+ = 474.2$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.46 (br d, $J=8.6$ Hz, 1H), 4.75 (br s, 1H), 4.31 (br s, 2H), 4.02 (s, 3H), 3.56 - 3.47 (m, 2H), 2.93 - 2.55 (m, 7H), 2.43 (s, 3H), 2.04 - 1.48 (m, 8H), 0.71 (br d, $J=10.8$ Hz, 6H). hLPA1 $\text{IC}_{50} = 69$ nM.	Example 241

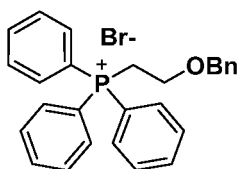
Example	Structure & Name	Analytical & Biology Data	Method
246	 (1<i>S</i>,3<i>S</i>)-3-((2-Methyl-6-(1-methyl-5-(2-((pyrrolidine-1-carbonyl)oxy)ethyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt	LC-MS, $[M+H]^+ = 458.3$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br s, 1H), 7.45 (br d, $J=8.6$ Hz, 1H), 4.75 (br s, 1H), 4.31 (t, $J=6.1$ Hz, 2H), 4.03 (s, 3H), 3.51 (br t, $J=6.0$ Hz, 2H), 3.21 – 2.62 (m, 5H), 2.42 (br s, 3H), 2.08 – 1.95 (m, 1H), 1.91 – 1.74 (m, 3H), 1.72 – 1.50 (m, 8H). hLPA1 $\text{IC}_{50} = 210$ nM.	Example 241
247	 (1<i>S</i>,3<i>S</i>)-3-((6-(5-(2-((Cyclobutyl(methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt	LC-MS, $[M+H]^+ = 472.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, $J=8.5$ Hz, 1H), 7.44 (d, $J=8.6$ Hz, 1H), 4.75 (br s, 1H), 4.31 (br t, $J=6.2$ Hz, 2H), 4.02 (s, 3H), 3.52 (br t, $J=5.7$ Hz, 2H), 3.24 – 3.15 (m, 1H), 2.68 – 2.56 (m, 4H), 2.43 (s, 3H), 2.08 – 1.38 (m, 14H). hLPA1 $\text{IC}_{50} = 41$ nM.	Example 241
248	 (1<i>S</i>,3<i>S</i>)-3-((6-(5-(2-(((Cyclobutyl-methyl)carbamoyl)oxy)ethyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid, TFA salt	LC-MS, $[M+H]^+ = 472.1$ ^1H NMR (500 MHz, DMSO-d_6) δ 7.49 (br s, 1H), 7.01 (br s, 1H), 4.75 (br s, 1H), 4.29 (br s, 2H), 4.02 (s, 3H), 3.54 – 3.24 (m, 2H), 3.00 – 2.94 (m, 2H), 2.71 – 2.63 (m, 2H), 2.35 (br s, 3H), 2.09 – 1.45 (m, 14H). hLPA1 $\text{IC}_{50} = 144$ nM.	Example 241

Example 249

(1*S*,3*S*)-3-((6-(5-(3-((Benzyl(methyl)carbamoyl)oxy)propyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid

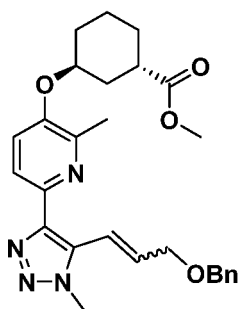


5 249A (2-(Benzyloxy)ethyl)triphenylphosphonium bromide



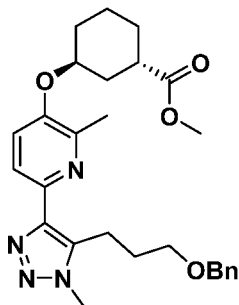
Benzyl 2-bromoethyl ether (0.78 mL, 4.96 mmol) was added to a solution of Ph_3P (1 g, 3.81 mmol) in toluene (7.63 mL) and the reaction was stirred at 105 °C for 18 h, then was cooled to rt. Diethyl ether (50 mL) was added, and the mixture was stirred for 15 min
 10 at rt; the precipitated product was collected by filtration, rinsed with ether and air-dried to afford the title product (1.46 g, 80 %) as a white solid. LC-MS, $[\text{M}]^+ = 397.1$. ^1H NMR (500 MHz, CDCl_3) δ 7.87 - 7.73 (m, 9H), 7.63 (td, $J=7.8, 3.3$ Hz, 6H), 7.27 - 7.19 (m, 3H), 6.92 (d, $J=6.6$ Hz, 2H), 4.36 (dt, $J=11.7, 5.7$ Hz, 2H), 4.27 (s, 2H), 4.11 - 4.01 (m, 2H).

15 249B. Methyl (1*S*,3*S*)-3-((6-(5-(3-(benzyloxy)prop-1-en-1-yl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylate



In a sealed tube was placed Example 249A (0.116 g, 0.243 mmol), Example 241A (0.058 g, 0.162 mmol), K_2CO_3 (0.067 g, 0.485 mmol), and THF (1.6 mL). The reaction was stirred at 115 °C for 2 h, then was cooled to rt. The mixture was diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was chromatographed (12 g Redisep[®] SiO_2 column, eluting with 0-100% EtOAc in Hex) to afford the title compound as a yellow solid (35 mg, 45 %) as a mixture of *cis/trans* isomers.

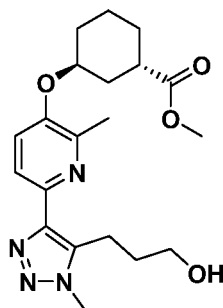
249C Methyl (1*S*,3*S*)-3-((6-(5-(3-(benzyloxy)propyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methyl pyridine-3-yl)oxy)cyclohexane-1-carboxylate.



To a solution of Example 249B (35 mg, 0.073 mmol) in MeOH (20 mL) under Ar was added 20% $Pd(OH)_2$ on carbon (10.31 mg, 0.015 mmol) and ammonium formate (93 mg, 1.47 mmol). The reaction mixture was stirred in a sealed tube at 65 °C for 18 h, then was cooled to rt. The reaction was filtered through a pad of Celite[®], rinsed with MeOH, and the filtrate was concentrated in vacuo. The crude material was purified by preparative HPLC using the following conditions: Column: Sunfire Prep C18 OBD 5um 30 x 100mm; Mobile Phase A: 10:90 MeCN: water with 0.1% TFA; Mobile Phase B: 90:10 MeCN: water with 0.1% TFA; Gradient: 20-100% B over 12 min; Flow: 40 mL/min. Fractions

containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (40 mg, 92 %) as a yellow solid. LC-MS, $[M+H]^+ = 479.3$.

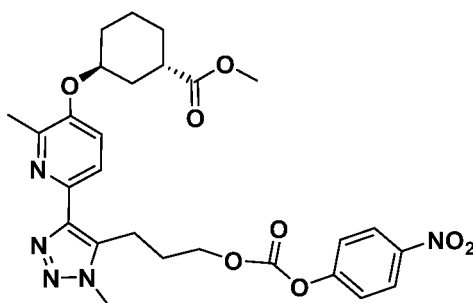
249D. Methyl (1*S*,3*S*)-3-(((6-(5-(3-hydroxypropyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methyl-pyridin-3-yl)oxy)cyclohexane-1-carboxylate.



To a solution of Example 249C (40 mg, 0.067 mmol) in EtOH (2 mL) and AcOH (1 mL) was added 10% Pd/C (7.2 mg, 6.8 μ mol), and H₂ gas was bubbled through the reaction mixture for a few minutes; the reaction was then stirred under H₂-balloon for 72 h. The reaction mixture was filtered through a pad of Celite®, rinsed with MeOH, and the combined filtrate/rinses were concentrated in vacuo. The crude material was purified by preparative HPLC using the following conditions: Column: Sunfire Prep C18 OBD 5u 30 x 100mm; Mobile Phase A: 10:90 MeCN: water with 0.1% TFA; Mobile Phase B: 90:10 MeCN: water with 0.1% TFA; Gradient: 20-100% B over 12 min; Flow: 40 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound 246D (23 mg, 68 %) as a colorless solid. LC-MS, $[M+H]^+ = 389.2$. ¹H NMR (500 MHz, CD₃OD) δ 8.10 - 7.98 (m, 2H), 5.02 - 4.96 (m, 1H), 4.15 (s, 3H), 3.71 (s, 3H), 3.62 (br t, $J=5.6$ Hz, 2H), 3.18 (br t, $J=7.2$ Hz, 2H), 2.91 - 2.83 (m, 1H), 2.71 (s, 3H), 2.20 - 2.10 (m, 1H), 2.07 - 1.90 (m, 5H), 1.85 - 1.65 (m, 4H).

20

249E Methyl (1*S*,3*S*)-3-((2-methyl-6-(1-methyl-5-(3-(((4-nitrophenoxy)carbonyl)oxy)propyl)-1*H*-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate



To a solution of Example 249D (21 mg, 0.042 mmol) and 4-nitrophenyl chloroformate (12.6 mg, 0.063 mmol) in THF (1 mL) was added pyridine (10 μ l, 0.13 mmol). The reaction was stirred at rt for 18 h, then was concentrated in vacuo. The crude product was chromatographed (4 g Redisep[®] SiO₂ column, eluting with 0-100% EtOAc in Hex) to afford the title compound (10 mg, 43 %) as a white solid. LC-MS, $[M+H]^+ = 554.2$.

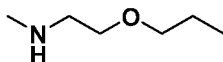
Example 249

To a solution of Example 249E (10 mg, 0.018 mmol) and DIEA (6.31 μ l, 0.036 mmol) in THF (1 mL) was added N-methyl-1-phenylmethanamine (2.2 mg, 0.018 mmol). After 1 h, water (0.5 mL) was added, followed by aq. LiOH (0.070 mL of a 2M solution, 0.139 mmol). The reaction mixture was stirred at rt for 18 h, after which the pH was adjusted with 1N aq. HCl to ~4 and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude material was purified by preparative HPLC using the following conditions: Column: Sunfire Prep C18 OBD 5u 30 x 100mm; Mobile Phase A: 10:90 MeCN: water with 0.1% TFA; Mobile Phase B: 90:10 MeCN: water with 0.1% TFA; Gradient: 20-100% B over 12 min; Flow: 40 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation, then re-purified by preparative HPLC using the following conditions: Column: Sunfire Prep C18 OBD 5u 30 x 100mm; Mobile Phase A: 10:90 MeOH: water with 0.1% TFA; Mobile Phase B: 90:10 MeOH: water with 0.1% TFA; Gradient: 20-100% B over 12 min; Flow: 40 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford the title compound (2.1 mg, 18 %) as a white solid. LC-MS, $[M+H]^+ = 522.3$. ¹H NMR (400 MHz, 60 $^{\circ}$ C, CD₃OD) δ 7.65 (br d, $J=8.4$ Hz, 1H), 7.32 (br d, $J=8.8$ Hz, 1H), 7.23 - 7.05 (m, 5H), 4.69 - 4.61 (m, 1H), 4.30 (s, 2H), 4.09 (t, $J=5.6$ Hz, 2H), 3.90

(br s, 3H), 3.16 - 3.08 (m, 2H), 2.75 - 2.63 (m, 4H), 2.39 (s, 3H), 2.04 - 1.89 (m, 3H), 1.89 - 1.75 (m, 3H), 1.72 - 1.49 (m, 4H). hLPA1 IC₅₀ = 122 nM.

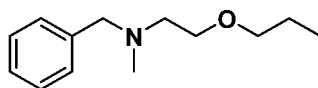
Synthesis of amine intermediate for the preparation of Example 250:

5 Intermediate 5. N-methyl-2-propoxyethan-1-amine



Intermediate 5A. N-benzyl-N-methyl-2-propoxyethan-1-amine

10



To a solution of 2-(benzyl(methyl)amino)ethan-1-ol (1 mL, 6.15 mmol) in dry DMF (5 mL) was added 60% NaH in mineral oil (0.369 g, 9.23 mmol) at 0 °C. After 1 h, 1-chloropropane (0.813 mL, 9.23 mmol) was added. The reaction mixture was stirred overnight at rt, then was quenched with ice water and extracted with EtOAc. The organic phase was washed with water and brine, dried (Na₂SO₄) and concentrated in vacuo. The crude oily product was chromatographed (24 g SiO₂; elution with EtOAc/ Hexane (continuous gradient from 0% to 100% over 10 min)) to give the free amine as an oil.

20 This oil was treated with 2.0 M HCl in ether to give N-benzyl-N-methyl-2-propoxyethan-1-amine HCl salt (1.2 g, 4.92 mmol, 80 % yield) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.67 - 7.61 (m, 2H), 7.47 - 7.43 (m, 3H), 4.34 - 4.20 (m, 2H), 4.04 - 3.93 (m, 2H), 3.46 (t, *J*=6.6 Hz, 2H), 3.34 - 3.27 (m, 1H), 3.14 - 3.06 (m, 1H), 2.74 (d, *J*=5.1 Hz, 3H), 1.65 - 1.59 (m, 2H), 0.93 (t, *J*=7.4 Hz, 3H)

25

Intermediate 5

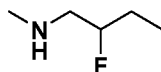
A mixture of Intermediate 5A (1.2 g, 4.92 mmol) and 20% Pd(OH)₂-C (0.346 g, 2.461 mmol) in EtOH (5 mL) was stirred at 60 °C under 1 atmosphere H₂ for 2 h, then was filtered and concentrated *in vacuo* to provide the title intermediate as the HCl salt

30 (0.72 g, 4.69 mmol, 95 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 9.41 (br

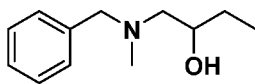
s, 2H), 3.81 (t, $J=4.8$ Hz, 2H), 3.44 (t, $J=6.6$ Hz, 2H), 3.24 - 3.11 (m, 2H), 2.77 (br t, $J=5.0$ Hz, 3H), 1.60 (sxt, $J=7.1$ Hz, 2H), 0.90 (t, $J=7.4$ Hz, 3H).

Synthesis of amine intermediate 6 for Examples 254 & 255:

5 Intermediate 6. 2-fluoro-N-methylbutan-1-amine

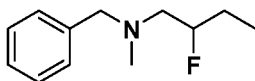


10 Intermediate 6A. 1-(benzyl(methyl)amino)butan-2-ol



A solution of N-methyl-1-phenylmethanamine (6.09 mL, 46.4 mmol) and 1,2-epoxybutane (1.0 mL, 11.6 mmol) in EtOH (50 mL) was stirred under reflux for 8 h, then was cooled to rt and concentrated in vacuo. The crude residue was chromatographed (80 g SiO₂; elution with MeOH/DCM (continuous gradient from 0% to 10% over 20 min) to give the title compound (500 mg, 2.59 mmol, 22.3 % yield) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 7.35 - 7.24 (m, 5H), 3.72 - 3.41 (m, 4H), 2.42 - 2.32 (m, 2H), 2.23 (s, 3H), 1.50 - 1.36 (m, 2H), 0.97 (t, $J=7.6$ Hz, 3H); $[M + H]^+ = 194.3$

20 Intermediate 6B. N-benzyl-2-fluoro-N-methylbutan-1-amine



25 DAST (0.697 mL in THF, 5.28 mmol) was added to a solution of Intermediate 6A (0.51 g, 2.64 mmol) in DCM (3 mL) at -78 °C and the reaction was stirred for 5 h at -78 °C and for 18 h at rt. Volatiles were concentrated in vacuo and the residue was carefully quenched with water (2 mL). The aqueous solution containing product was purified by prepHPLC (Sunfire C18 30 x 100 mm-regenerated column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 0% B to 100% B over 10 min + 2

min hold time at 100% B, where A = 90:10:0.1 H₂O:MeCN:TFA and B = 90:10:0.1 MeCN:H₂O:TFA) and appropriate fractions were concentrated to obtain an oil. The residue was treated with 2.0 M HCl in ether (3.61 mL, 7.22 mmol) to give the HCl salt of the title compound (0.22 g, 1.127 mmol, 42.7 % yield) as a clear oil. ¹H NMR (500 MHz, CD₃OD) δ 7.54 (s, 5H), 5.12 - 4.91 (m, 1H), 4.68 - 4.22 (m, 2H), 3.56 - 3.41 (m, 2H), 3.01 - 2.83 (m, 3H), 1.84 - 1.60 (m, 2H), 1.06 (q, *J*=7.7 Hz, 3H); ¹⁹F NMR (471 MHz, METHANOL-*d*₄) δ -186.78 (s), -188.25(s); [M + H]⁺ = 196.3

Intermediate 6.

A mixture of Intermediate 6B (0.22 g, 0.95 mmol) and 20% Pd(OH)₂-C (0.067 g, 0.475 mmol) in EtOH (5 mL) was stirred at 60 °C under 1 atmosphere of H₂ for 2 h. The mixture was filtered and concentrated *in vacuo* to provide the title compound as the HCl salt (0.099 g, 9.41 mmol, 99 % yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 10.06 - 9.40 (m, 2H), 5.34 - 4.94 (m, 1H), 3.38 - 3.02 (m, 2H), 2.81 (br s, 3H), 1.75 (br d, *J*=1.5 Hz, 2H), 1.04 (br t, *J*=6.2 Hz, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ: -185.22 (br s, F).

Intermediate 7. 4-fluoro-N-methylpentan-1-amine (for the synthesis of Example 256)



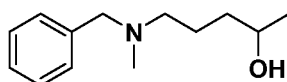
7A. N-benzyl-4-hydroxy-N-methylpentanamide



N-methyl-1-phenylmethanamine (5.78 mL, 44.9 mmol) was added to a mixture of 5-methyl dihydrofuran-2(3H)-one (1.426 mL, 14.98 mmol) and toluene (20 mL), and NaOMe solution (sodium (1.033 g, 44.9 mmol) added to MeOH (15 mL)) was added dropwise at 20 to 30°C, followed by stirring for 18 h at rt. The reaction was quenched by addition of ice water (20 mL) and HOAc (3.43 mL, 60 mmol) was added dropwise. The

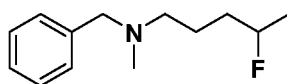
aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with water and concentrated in vacuo. The crude oily product was chromatographed (40 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 100% over 10 min)) to give the title compound (1.5 g, 6.78 mmol, 45.2 % yield) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.13 (m, 5H), 4.63 - 4.53 (m, 2H), 3.85 (dddd, *J*=14.0, 8.0, 6.2, 4.2 Hz, 1H), 3.02 (dd, *J*=7.4, 4.5 Hz, 1H), 2.98 - 2.91 (m, 3H), 2.66 - 2.45 (m, 2H), 1.97 - 1.70 (m, 2H), 1.21 (dd, *J*=17.6, 6.4 Hz, 3H); [M + H]⁺ = 222.2.

10 7B. 5-(benzyl(methyl)amino)pentan-2-ol



Intermediate 7A (1.5 g, 6.78 mmol) was added to a suspension of LAH (4.07 mL of a 2.0 M solution in THF; 8.13 mmol) in THF (50 mL). The mixture was heated at reflux for 18 h, then was cooled to 0° C. Brine (~1 mL) was carefully added until no more gas was generated. The solids were filtered off, and the filtrate was concentrated in vacuo. The crude residue was chromatographed (12 g SiO₂; elution with MeOH/DCM (continuous gradient from 0% to 10% over 20 min) to give the title compound (1.35 g, 6.51 mmol, 96 % yield) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 7.40 - 7.25 (m, 5H), 3.84 - 3.73 (m, 1H), 3.56 (q, *J*=12.7 Hz, 2H), 2.59 - 2.51 (m, 1H), 2.49 - 2.39 (m, 1H), 2.18 (s, 3H), 1.82 - 1.67 (m, 3H), 1.50 - 1.40 (m, 1H), 1.22 (d, *J*=6.3 Hz, 3H); [M + H]⁺ = 208.3.

25 7C. N-benzyl-4-fluoro-N-methylpentan-1-amine



DAST (1.03 mL in THF, 7.81 mmol) was added to a solution of Intermediate 7B (0.81 g, 3.91 mmol) in DCM (3 mL) at -78 °C and the reaction was stirred for 5 h at -78 °C and for 18 h at rt. The reaction was concentrated in vacuo and carefully quenched

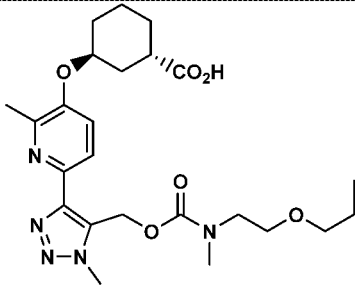
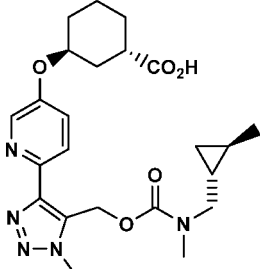
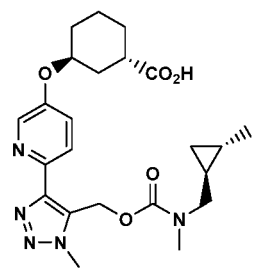
with water (2 mL). The aqueous solution was purified by preparative HPLC (Sunfire C18 30 x 100 mm-regenerated column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 0% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeCN:TFA and B = 90:10:0.1 MeCN:H₂O:TFA) and
5 appropriate fractions were concentrated to give an oil. The residue was treated with 2.0 M HCl in ether (3.61 mL, 7.22 mmol) to give the title compound as the HCl salt (0.12 g, 0.488 mmol, 12.50 % yield) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 12.21 (br s, 1H), 7.62 (br s, 2H), 7.50 - 7.41 (m, 3H), 4.80 - 4.55 (m, 1H), 4.32 - 4.15 (m, 2H), 3.23 - 2.83 (m, 2H), 2.81 - 2.64 (m, 3H), 2.21 - 1.94 (m, 2H), 1.78 - 1.55 (m, 2H), 1.40 - 1.27
10 (m, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ -173.65 (d, *J*=38.9 Hz, F); [M + H]⁺ = 210.2

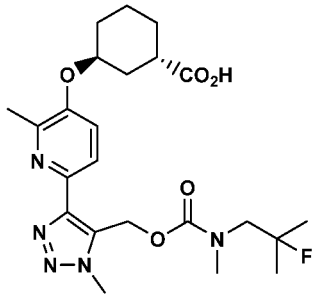
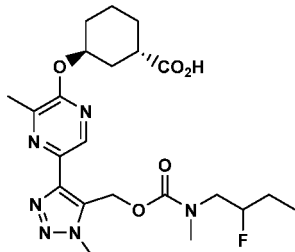
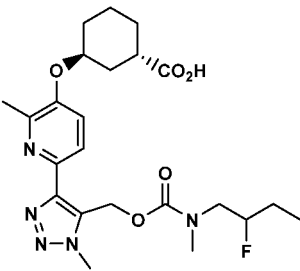
Intermediate 7

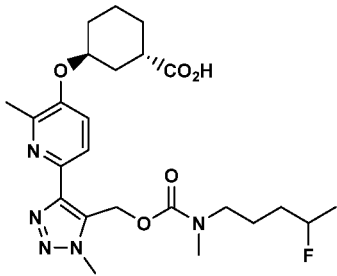
A mixture of Intermediate 7C (0.12 g, 0.488 mmol) and 20% Pd(OH)₂-C (0.034 g, 0.24 mmol) in EtOH (5 mL) was stirred at 60 °C under 1 atmosphere H₂ for 2 h. The
15 reaction was filtered and concentrated *in vacuo* to provide the title compound as the HCl salt (0.05 g, 0.321 mmol, 65.8 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 9.51 (br s, 2H), 4.83 - 4.62 (m, 1H), 3.01 (br s, 2H), 2.70 (br s, 3H), 2.13 - 1.94 (m, 2H), 1.81 - 1.65 (m, 2H), 1.41 - 1.29 (m, 3H); ¹⁹F NMR (471 MHz, CDCl₃) δ -173.53 (s, 1F).

20

25

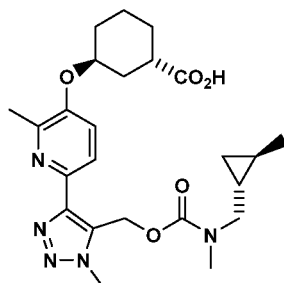
Example	Structure & Name	Analytical & Biology Data	Method
250	 (1S,3S)-3-(((2-methyl-6-(1-methyl-5-(((methyl(2-propoxyethyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 490.3$; 1H NMR (500 MHz, DMSO-d_6) δ 7.85 (br s, 1H), 7.47 (d, $J=8.6$ Hz, 1H), 5.66 (br s, 2H), 4.77 (br s, 1H), 4.10 (s, 3H), 2.83 (br s, 3H), 2.71 - 2.61 (m, 1H), 2.43 (s, 3H), 2.08 - 1.98 (m, 1H), 1.91 - 1.76 (m, 3H), 1.72 - 1.34 (m, 6H), 0.79 (br s, 3H), 6 protons are in water suppression area LPA1 $IC_{50} = 314$ nM	Example 1
251	 (1S,3S)-3-(((6-(1-methyl-5-(((methyl(((1R,2R)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 458.1$; 1H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, $J=2.5$ Hz, 1H), 8.24 (d, $J=8.8$ Hz, 1H), 7.89 - 7.79 (m, 1H), 5.54 (s, 2H), 4.84 (br s, 1H), 4.23 (br s, 3H), 3.23 - 3.15 (m, 1H), 3.14 - 2.98 (m, 1H), 2.94 (br s, 4H), 2.19 - 2.01 (m, 2H), 1.98 - 1.75 (m, 5H), 1.73 - 1.61 (m, 1H), 1.03 (br s, 3H), 0.70 - 0.51 (m, 2H), 0.42 - 0.22 (m, 2H) LPA1 $IC_{50} = 27$ nM	Example 3
252	 (1S,3S)-3-(((6-(1-methyl-5-(((methyl(((1S,2S)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 458.1$; 1H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, $J=1.9$ Hz, 1H), 8.23 (d, $J=8.8$ Hz, 1H), 7.82 (br d, $J=8.0$ Hz, 1H), 5.54 (s, 2H), 4.84 (br s, 1H), 4.23 (br s, 3H), 3.24 - 3.14 (m, 1H), 3.14 - 2.97 (m, 1H), 2.93 (br s, 4H), 2.19 - 2.00 (m, 2H), 1.98 - 1.61 (m, 6H), 1.02 (br s, 3H), 0.69 - 0.50 (m, 2H), 0.42 - 0.20 (m, 2H) LPA1 $IC_{50} = 29$ nM	Example 3

Example	Structure & Name	Analytical & Biology Data	Method
253	 (1S,3S)-3-((6-(5-(((2-fluoro-2-methylpropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 478.1$; ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br d, $J=8.5$ Hz, 1H), 7.47 (br d, $J=8.6$ Hz, 1H), 5.67 (br s, 4H), 4.77 (br s, 2H), 4.10 (s, 4H), 2.86 (br s, 2H), 2.65 (br t, $J=10.1$ Hz, 1H), 2.42 (s, 3H), 2.08 - 1.99 (m, 1H), 1.91 - 1.75 (m, 3H), 1.73 - 1.44 (m, 4H), 1.37 - 0.97 (m, 6H) 3 protons are in water suppression area LPA1 $\text{IC}_{50} = 134$ nM	Example 1
254	 (1S,3S)-3-((5-(5-(((2-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-3-methylpyrazin-2-yl)oxy)cyclohexane-1-carboxylic acid; mixture of diastereomers	LCMS; $[M + H]^+ = 479.1$; ^1H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 5.71 - 5.48 (m, 2H), 5.39 (br s, 1H), 4.73 - 4.21 (m, 1H), 4.11 (s, 3H), 3.57 - 3.19 (m, 2H), 2.90 - 2.74 (m, 3H), 2.64 (br t, $J=11.1$ Hz, 1H), 2.45 (s, 3H), 2.19 - 2.04 (m, 1H), 1.96 - 1.72 (m, 3H), 1.70 - 1.24 (m, 6H), 0.97 - 0.60 (m, 3H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.42 (br s, TFA), -185.33 (br d, $J=97.1$ Hz, F) LPA1 $\text{IC}_{50} = 132$ nM	
255	 (1S,3S)-3-((6-(5-(((2-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid; mixture of diastereomers	LCMS; $[M + H]^+ = 478.2$; ^1H NMR (500 MHz, DMSO-d_6) δ 7.85 (br s, 1H), 7.47 (br d, $J=8.2$ Hz, 1H), 5.76 - 5.51 (m, 2H), 4.77 (br s, 1H), 4.69 - 4.20 (m, 1H), 4.09 (s, 3H), 3.60 - 3.20 (m, 2H), 2.94 - 2.73 (m, 3H), 2.62 (br s, 1H), 2.40 (br s, 3H), 2.07 - 1.19 (m, 10H), 0.98 - 0.55 (m, 3H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.54 (s, TFA), -185.49 (s) LPA1 $\text{IC}_{50} = 57$ nM	Example 1

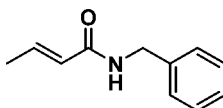
Example	Structure & Name	Analytical & Biology Data	Method
256	 (1S,3S)-3-((6-(5-(((4-fluoropentyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS; $[M + H]^+ = 492.3$; 1H NMR (500 MHz, DMSO-d_6) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.45 (br d, $J=8.5$ Hz, 1H), 5.62 (br d, $J=13.7$ Hz, 2H), 4.85 - 4.29 (m, 2H), 4.08 (s, 3H), 3.25 - 3.03 (m, 2H), 2.83 - 2.68 (m, 3H), 2.62 (br t, $J=10.2$ Hz, 1H), 2.40 (s, 3H), 1.99 (br d, $J=13.7$ Hz, 1H), 1.90 - 0.97 (m, 11H), 0.84 (br t, $J=7.2$ Hz, 3H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.75 (s, TFA), -170.59 (br d, $J=65.9$ Hz, F) LPA1 $IC_{50} = 17$ nM	Example 1

Example 257

(1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(((1R,2R)-2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



257A. (E)-N-benzylbut-2-enamide

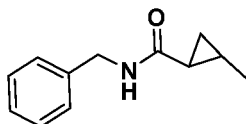


- 10 EDC (36.7 g, 192 mmol) was added portionwise to a solution of crotonic acid (15.0 g, 174 mmol), benzyl amine (21.0 mL, 192 mmol) and DIPEA (33.5 mL, 192 mmol) in DCM (300 mL). The reaction mixture was stirred overnight and then poured onto 10% aq. $KHSO_4$ (250 mL) and extracted with EtOAc (100 mL). The organic layer was washed once again with 10% aq. $KHSO_4$ followed by brine (150 mL), dried (Na_2SO_4)

and concentrated in vacuo to give the title compound as a white solid (25 g, 143 mmol, 82 % yield). $[M + H]^+ = 176.2$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.40 - 7.20 (m, 5H), 6.98 - 6.82 (m, 1H), 5.84 (br dd, $J=15.1, 1.7$ Hz, 2H), 4.52 (d, $J=5.8$ Hz, 2H), 1.87 (dd, $J=6.9, 1.7$ Hz, 3H)

5

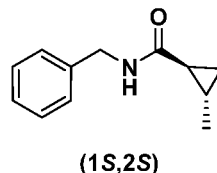
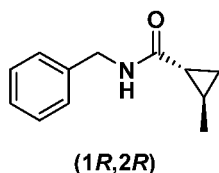
257B. N-benzyl-2-methylcyclopropanecarboxamide



In an Erlenmeyer flask containing Et_2O (50 mL) and aq. 40% KOH (5 mL) was added N-methyl-N'-nitro-N-nitrosoguanidine (504 mg, 3.42 mmol) portionwise (with vigorous stirring) over 15 min at 0 °C. Upon complete addition, stirring was stopped and the aqueous layer was separated. The ether layer was dried with KOH pellets and allowed to stand for 5 min, then decanted into a third flask with KOH pellets and then poured onto a THF solution (2 mL) containing Example 257A (300 mg, 1.712 mmol). $\text{Pd}(\text{OAc})_2$ (3.84 mg, 0.017 mmol) was subsequently added and the reaction allowed to warm to rt and stirred for 1 h at rt. The reaction was concentrated in vacuo, and the crude oil was chromatographed (12 g SiO_2 ; elution with EtOAc /Hexane (continuous gradient from 0% to 50% over 20 min) to give the title compound (310 mg, 1.61 mmol, 94 % yield) as a white solid. $[M + H]^+ = 190.2$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.37 - 7.26 (m, 5H), 5.82 (br s, 1H), 4.44 (dd, $J=5.6, 2.3$ Hz, 2H), 1.46 - 1.32 (m, 1H), 1.22 - 1.15 (m, 1H), 1.12 - 1.03 (m, 4H), 0.57 (ddd, $J=7.9, 6.2, 3.7$ Hz, 1H)

20

257C (1R,2R)-N-benzyl-2-methylcyclopropane-1-carboxamide and 257D (1S,2S)-N-benzyl-2-methylcyclopropane-1-carboxamide

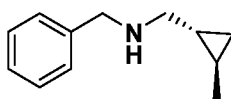


25

Example 257B (2.0 g, 10.6 mmol) was separated by chiral preparative HPLC (Instrument: Berger MG II (CTR-L409-PSFC1), Column: Chiralpak ID, 21 x 250 mm, 5

micron, Mobile Phase: 15% IPA / 85% CO₂, Flow Conditions: 45 mL/min, 150 Bar, 40°C, Detector Wavelength: 220 nm, Injection Details: 0.25 mL of an ~200 mg/mL in IPA) to give Example 257C (0.9 g, 4.76 mmol, 45.0 % yield, 99.0% ee) and Example 257D (0.9 g, 4.76 mmol, 45.0 % yield, 99.0% ee) as white solids. The absolute stereochemistry of these two isomers was previously determined in the literature reference *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1788.

257E. N-benzyl-1-((1R,2R)-2-methylcyclopropyl)methanamine,



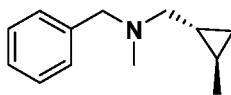
(1R,2R)

To a solution of Example 257C (0.90 g, 4.76 mmol) in THF (50 mL) was added BH₃.THF (23.8 mL of a 1M solution in THF, 23.8 mmol) dropwise. Upon completion of the addition (10 min), the mixture was heated at reflux for 5 h, then cooled to rt and quenched via successive addition of MeOH (2 mL) and 1N aq. HCl dropwise (10 mL).

The resulting solution was stirred at 50 °C for 1 h and then partitioned between water and Et₂O (50 mL each). The aqueous layer was neutralized with 7N aq. KOH and extracted with DCM (3 x 10 mL). The organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The oily product was diluted with EtOAc and treated with HCl gas. The resulting solids were filtered, washed with hexane and dried to give the title compound (HCl salt; 0.9 g, 4.25 mmol, 89 % yield) as a white solid.

[M + H]⁺ = 176.2; ¹H NMR (400 MHz, CD₃OD) δ 7.56 - 7.43 (m, 5H), 4.21 (s, 2H), 3.02 - 2.90 (m, 2H), 1.12 (d, *J*=5.5 Hz, 3H), 0.93 - 0.73 (m, 2H), 0.59 (dt, *J*=8.0, 5.0 Hz, 1H), 0.50 (dt, *J*=7.8, 5.3 Hz, 1H)

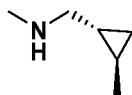
257F. N-benzyl-N-methyl-1-((1R,2R)-2-methylcyclopropyl)methanamine



(1R,2R)

A solution of Example 257E (0.90 g, 5.13 mmol), 36% aq. formaldehyde solution (1.97 mL, 25.7 mmol), and HOAc (3 mL, 52.4 mmol) in MeOH (10 mL) was stirred at rt for 5 min. NaBH(OAc)₃ (2.177 g, 10.27 mmol) was then added. The reaction mixture was stirred at rt for 20 min and then concentrated in vacuo and the residue was partitioned
5 between DCM (20 mL) and 1N NaOH (50 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was treated with 2.0 M HCl in ether (3 mL, 6.0 mmol) to give the title compound (HCl salt; 0.97 g, 4.30 mmol, 84 % yield) as a white solid. $[M + H]^+ = 176.2$; ¹H NMR (400 MHz, CD₃OD) δ 7.55 - 7.51 (m, 5H), 4.49 (dd, $J=13.0, 7.3$ Hz, 1H), 4.24 (br d, $J=13.2$ Hz, 1H), 3.22 - 3.14 (m, 1H), 3.02 (dt, $J=13.3, 7.8$
10 Hz, 1H), 2.85 (d, $J=5.9$ Hz, 3H), 1.15 (d, $J=5.7$ Hz, 3H), 0.94 - 0.79 (m, 2H), 0.66 - 0.53 (m, 2H)

257G. N-methyl-1-((1R,2R)-2-methylcyclopropyl)methanamine



(1R,2R)

A mixture of Example 257F HCl salt (0.97 g, 4.30 mmol) and 20% Pd(OH)₂-C (0.1 g, 0.712 mmol) in EtOH (40 mL) was stirred at 60 °C under 1 atmosphere of H₂ for 2 h. The reaction was filtered and concentrated *in vacuo* to provide the title compound
20 (HCl salt, 0.54 g, 3.98 mmol, 93 % yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 2.91 (d, $J=7.3$ Hz, 2H), 2.71 (s, 3H), 1.12 (d, $J=5.9$ Hz, 3H), 0.92 - 0.75 (m, 2H), 0.59 (dt, $J=8.4, 4.9$ Hz, 1H), 0.48 (dt, $J=8.0, 5.1$ Hz, 1H)

Example 257

To a solution of Example 1F (30 mg, 0.054 mmol) in DCM (1 mL) was added Example 257G HCl salt (7.4 mg, 0.054 mmol) and DIPEA (0.028 mL, 0.163 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated in vacuo. The residue was stirred with 1.0 M aq. NaOH (0.54 mL, 0.54 mmol) in THF (1 mL)/MeOH (0.2 mL) at rt
30 for 18 h, then concentrated in vacuo and purified by preparative HPLC (Xbridge C18 5u

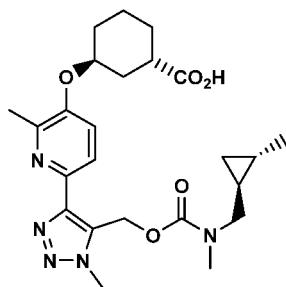
OBD 19X100mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 15% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeCN:TFA and B = 90:10:0.1 MeCN:H₂O:TFA) to give the title compound (TFA salt; 26 mg, 0.044 mmol, 81 % yield) as a yellowish oil.

- 5 [M + H]⁺ = 472.1; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J*=8.8 Hz, 1H), 7.66 (br t, *J*=9.9 Hz, 1H), 5.67 - 5.53 (m, 2H), 4.80 (br s, 1H), 4.18 (s, 3H), 3.28 - 2.91 (m, 5H), 2.86 (br s, 1H), 2.66 (s, 3H), 2.15 - 1.56 (m, 8H), 1.01 (br dd, *J*=12.1, 5.1 Hz, 3H), 0.72 - 0.46 (m, 2H), 0.43 - 0.13 (m, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δ -75.88 (s, TFA). hLPA1 IC₅₀ = 18 nM

10

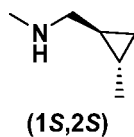
Example 258.

(1R,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(((1S,2S)-2-methylcyclopropyl)methyl) carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



15

258A. N-methyl-1-((1S,2S)-2-methylcyclopropyl)methanamine



20

The same synthetic sequence to prepare Example 257G (from Example 257C) was used to prepare Example 258A from Example 257D (HCl salt; 0.53 g, 3.91 mmol, 91 % yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 2.91 (d, *J*=7.3 Hz, 2H), 2.75 - 2.70 (m, 3H), 1.12 (d, *J*=5.7 Hz, 3H), 0.95 - 0.76 (m, 2H), 0.59 (dt, *J*=8.5, 4.9 Hz, 1H), 0.48 (dt, *J*=8.2, 5.1 Hz, 1H)

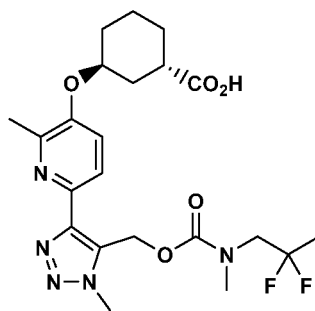
25

Example 258.

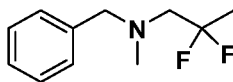
To a solution of Example 1F (30 mg, 0.054 mmol) in DCM (1 mL) added Example 258A HCl salt (7.35 mg, 0.054 mmol) and DIPEA (0.028 mL, 0.163 mmol). The reaction mixture was stirred at rt for 2 h, then was concentrated in vacuo. The residue was stirred with 1.0 M aq. NaOH (0.542 mL, 0.542 mmol) in THF (1 mL)/MeOH (0.2 mL) at rt for 18 h and then purified by preparative HPLC (Xbridge C18 5u OBD 19X100mm column; detection at 220 nm; flow rate = 20 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:MeCN:TFA and B = 90:10:0.1 MeCN:H₂O:TFA) to give the title compound (TFA salt, 27 mg, 0.046 mmol, 84 % yield) as a yellowish oil. [M + H]⁺ = 472.1; ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J*=8.8 Hz, 1H), 7.63 (br t, *J*=9.6 Hz, 1H), 5.72 - 5.51 (m, 2H), 4.79 (br d, *J*=3.1 Hz, 1H), 4.18 (s, 3H), 3.29 - 2.80 (m, 6H), 2.65 (s, 3H), 2.11 - 1.98 (m, 2H), 1.97 - 1.56 (m, 6H), 1.01 (br dd, *J*=13.4, 5.1 Hz, 3H), 0.69 - 0.16 (m, 4H). hLPA1 IC₅₀ = 19 nM

Example 259

(1*S*,3*S*)-3-(((6-(5-(((2,2-difluoropropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



259A. N-benzyl-2,2-difluoro-N-methylpropan-1-amine

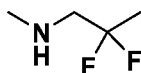


To a solution of 1-(benzyl(methyl)amino)propan-2-one (1.28 g, 7.22 mmol) and DAST (2.86 mL, 21.66 mmol) in DCM (12 mL) was added CsF (0.329 g, 2.166 mmol)

portionwise, followed by a few drops of TFA at rt. The reaction mixture was stirred for 18 h at rt, then was quenched with satd aq. NaHCO₃. The aqueous layer was extracted with DCM (50 mL X 3). The combined organic extracts were washed with water, brine, dried (MgSO₄) and concentrated in vacuo. The crude oily product was chromatographed (12 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 50% over 10 min) and then further purified by preparative HPLC to give a clear oil. This material was treated with 2.0 M HCl in ether (3.61 mL, 7.22 mmol) to give the title compound (HCl salt, 334 mg, 1.417 mmol, 19.6 % yield) as a white solid.

[M + H]⁺ = 482.3; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dt, *J*=3.8, 2.8 Hz, 2H), 7.55 - 7.38 (m, 3H), 4.56 - 4.18 (m, 2H), 3.65 - 3.15 (m, 2H), 2.94 (s, 3H), 1.80 (t, *J*=19.3 Hz, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ -87.77 to -91.55 (m, F)

259B. 2,2-difluoro-N-methylpropan-1-amine



A mixture of Example 259A (HCl salt; 0.33 g, 1.40 mmol) and 20% Pd(OH)₂-C (0.10 g, 0.712 mmol) in EtOH (40 mL) was stirred at 60 °C under 1 atmosphere H₂ for 2 h. Filtration and concentration *in vacuo* provided 2,2-difluoro-N-methylpropan-1-amine (HCl salt, 200 mg, 1.37 mmol, 98 % yield) as a white solid.

¹H NMR (500 MHz, CD₃OD) δ 3.63 (t, *J*=14.9 Hz, 2H), 2.81 (s, 3H), 1.79 (t, *J*=19.1 Hz, 3H); ¹⁹F NMR (471 MHz, CD₃OD) δ -98.01 (s)

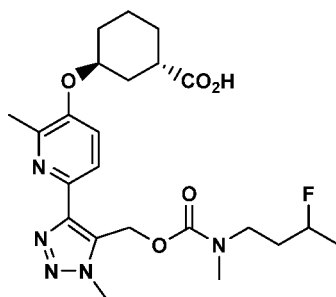
Example 259.

To a solution of Example 1F (30 mg, 0.054 mmol) in DCM (1 mL) added Example 259B (HCl salt; 15.78 mg, 0.108 mmol) and DIPEA (0.047 mL, 0.271 mmol). The reaction mixture was stirred at 50 °C for 18 h and then concentrated in vacuo. The residue was stirred with 1.0 M aq. NaOH (0.271 mL, 0.271 mmol) in THF (1 mL)/MeOH (0.2 mL) at rt for 18 h and then purified by preparative LC/MS (Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 MeCN:H₂O with 10-mM NH₄OAc; Mobile Phase B: 95:5 MeCN:H₂O with 10-mM NH₄OAc; Gradient: 15-55% B over 20 min, then a 4-min hold at 100% B; Flow: 20 mL/min) to give the title compound (TFA

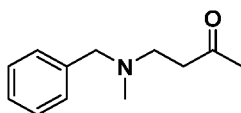
salt; 9.3 mg, 0.015 mmol, 27.4 % yield) as a yellowish oil. $[M + H]^+ = 482.3$; ^1H NMR (500 MHz, DMSO- d_6) δ 7.85 (br d, $J=7.9$ Hz, 1H), 7.49 (br d, $J=8.5$ Hz, 1H), 5.70 (br d, $J=18.3$ Hz, 2H), 4.79 (br s, 1H), 4.11 (br s, 3H), 3.76 - 3.52 (m, 1H), 2.95 - 2.78 (m, 3H), 2.64 (br t, $J=10.4$ Hz, 1H), 2.42 (s, 3H), 2.03 (br d, $J=13.7$ Hz, 1H), 1.92 - 1.74 (m, 3H), 1.69 - 1.34 (m, 8H); ^{19}F NMR (471 MHz, DMSO- d_6) δ -73.67 (s, TFA), -93.07 (br d, $J=64.2$ Hz). hLPA1 $\text{IC}_{50} = 134$ nM

Example 260.

(1S,3S)-3-((6-(5-(((3-fluorobutyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



260A. 4-(benzyl(methyl)amino)butan-2-one

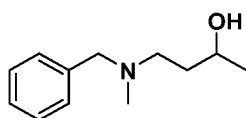


15

A mixture of N-methyl-1-phenylmethanamine (2.57 mL, 20 mmol), paraformaldehyde (0.901 g, 30.0 mmol) and conc. HCl (1.67 mL, 20.0 mmol) in iPrOH (2 mL) and acetone (50 mL) was stirred under reflux overnight and then concentrated in vacuo. The residue was diluted with water, basified to pH 14 with 1 N aq. NaOH solution (33.4 mL, 33.4 mmol) and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the title compound (4.0 g, 20.9 mmol, 94 % yield), which was used directly in the next reaction. $[M + H]^+ = 192.2$; ^1H NMR (400 MHz, CDCl_3) δ 7.34 - 7.22 (m, 5H), 3.49 (s, 2H), 2.74 - 2.67 (m, 2H), 2.66 - 2.58 (m, 2H), 2.19 (s, 3H), 2.14 (s, 3H)

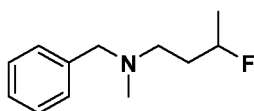
25

260B. 4-(benzyl(methyl)amino)butan-2-ol



NaBH₄ (2.37 g, 62.7 mmol) was added to a solution of Example 260A (4.0 g, 20.9 mmol) in MeOH (90 mL) at 0°C under N₂. The reaction mixture was stirred for 1 h at 0°C; water was then added at 0°C and the mixture was concentrated in vacuo. The residue
 5 was dissolved in EtOAc, washed with water, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; elution with isocratic 10% EtOH/CHCl₃) to give the title compound (3.5 g, 18.11 mmol, 87 % yield) as a light yellowish oil. [M + H]⁺ = 194.2; ¹H NMR (400 MHz, CDCl₃) δ 7.35 - 7.27 (m, 5H), 3.99 - 3.86 (m, 1H), 3.72 - 3.31 (m, 2H), 2.76 (td, *J*=12.0, 3.3 Hz, 1H), 2.59 - 2.48 (m, 1H), 2.22 (s, 3H),
 10 1.72 - 1.61 (m, 1H), 1.54 - 1.45 (m, 1H), 1.15 (d, *J*=6.2 Hz, 3H)

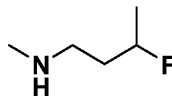
260C. N-benzyl-3-fluoro-N-methylbutan-1-amine



15

DAST (1.367 mL, 10.35 mmol) was added to a solution of Example 260B (1.0 g, 5.17 mmol) in DCM (5 mL) at -78 °C and the reaction was stirred for 5 h at -78 °C and 18 h at rt, after which it was quenched with sat. aq. NaHCO₃ (50 mL). The aqueous layer was extracted with DCM (20 mL x 3), and the combined organic extracts were dried
 20 (MgSO₄) and concentrated in vacuo. The crude oil was purified by preparative HPLC (Sunfire C18 30 x 100 mm-regenerated column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 0% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeCN:TFA and B = 90:10:0.1 MeCN:H₂O:TFA) and appropriate fractions were concentrated in vacuo to give an oil. This product was treated
 25 with 2.0 M HCl in ether (3.61 mL, 7.22 mmol) to give the title compound (HCl salt; 0.15 g, 0.647 mmol, 12.5 % yield) as a white solid. [M + H]⁺ = 196.2; ¹H NMR (400 MHz, CDCl₃) δ 7.69 - 7.54 (m, 2H), 7.50 - 7.34 (m, 3H), 4.97 - 4.57 (m, 1H), 4.39 - 3.96 (m, 2H), 3.38 - 3.21 (m, 1H), 3.08 - 2.88 (m, 1H), 2.77 - 2.64 (m, 3H), 2.57 - 1.96 (m, 2H), 1.54 - 1.29 (m, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ -176.04 (s), -176.11 (s)

260D.



5

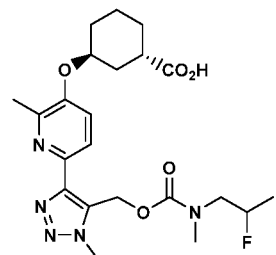
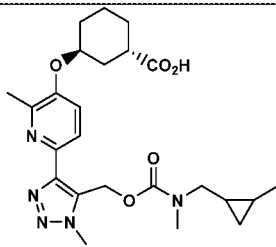
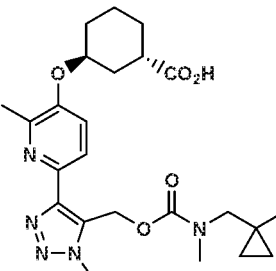
A mixture of Example 260C (HCl salt; 0.15 g, 0.647 mmol) and 20% Pd(OH)₂-C (0.045 g, 0.324 mmol) in EtOH (5 mL) was stirred at 60 °C under 1 atmosphere H₂ for 2 h. Filtration and concentration *in vacuo* provided the title compound (HCl salt; 0.075 g, 0.530 mmol, 82 % yield) as a white solid.

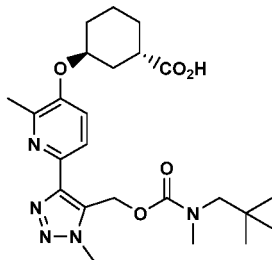
10 ¹H NMR (400 MHz, CDCl₃) δ 5.01 - 4.71 (m, 1H), 3.13 (br s, 2H), 2.72 (br s, 3H), 2.33 - 2.06 (m, 2H), 1.53 - 1.25 (m, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ -175.47 (s, 1F)

Example 260

To a solution of Example 1F (30 mg, 0.054 mmol) in DCM (1 mL) was added
 15 Example 260D (HCl salt; 15.4 mg, 0.11 mmol) and DIPEA (0.047 mL, 0.271 mmol). The reaction mixture was stirred at rt for 1 h, then was concentrated in vacuo. The residue was stirred with 1.0 M aq. NaOH (0.271 mL, 0.271 mmol) in THF (1 mL)/MeOH (0.2 mL) at rt for 18 h and then was purified by preparative HPLC (Sunfire C18 30 x 100 mm-regenerated column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient
 20 from 30% B to 100% B over 10 min + 2 min hold time at 100% B, where A = 90:10:0.1 H₂O:MeCN:TFA and B = 90:10:0.1 MeCN:H₂O: TFA) to give the title compound (TFA salt; 24 mg, 0.040 mmol, 73.4 % yield) as a yellowish oil.

[M + H]⁺ = 478.1; ¹H NMR (500 MHz, CDCl₃) δ 8.18 (br d, *J*=8.5 Hz, 1H), 8.00 (br d, *J*=8.0 Hz, 1H), 5.57 - 5.42 (m, 2H), 4.90 (br s, 1H), 4.78 - 4.51 (m, 1H), 4.23 (s, 3H), 3.55
 25 - 3.41 (m, 2H), 3.04 - 2.93 (m, 3H), 2.91 - 2.82 (m, 1H), 2.82 - 2.75 (m, 4H), 2.23 - 2.06 (m, 1H), 2.06 - 1.95 (m, 1H), 1.95 - 1.77 (m, 6H), 1.69 (br s, 1H), 1.42 - 1.31 (m, 3H); ¹⁹F NMR (471 MHz, CDCl₃) δ -76.03 (br s, TFA), -176.02 (dd, *J*=135.2, 9.3 Hz, F). hLPA1 IC₅₀ = 50 nM.

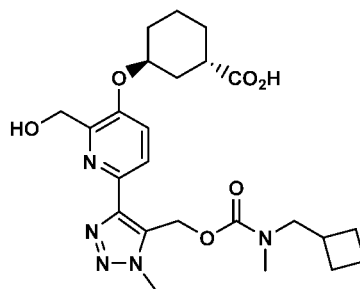
Example	Structure & Name	Analytical & Biology Data	Method
261	 (1S,3S)-3-((6-(5-(((2-fluoropropyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS: $[M + H]^+ = 464.0$; 1H NMR (500 MHz, $CDCl_3$) δ 8.18 - 8.05 (m, 1H), 7.82 - 7.68 (m, 1H), 5.73 - 5.46 (m, 2H), 4.96 - 4.69 (m, 2H), 4.22 (br d, $J=12.9$ Hz, 3H), 3.03 (br d, $J=7.2$ Hz, 3H), 2.96 - 2.84 (m, 1H), 2.78 - 2.63 (m, 3H), 2.21 - 1.53 (m, 9H), 1.41 - 1.22 (m, 4H); ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.91 (br s, TFA), -175.36 to -181.71 (m, 1F) LPA1 $IC_{50} = 145$ nM	Example 1
262	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((2-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid; mixture of diastereomers	LCMS: $[M + H]^+ = 472.2$; 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, $J=8.8$ Hz, 1H), 7.94 (br d, $J=9.0$ Hz, 1H), 5.57 - 5.40 (m, 2H), 4.87 (br s, 1H), 4.21 (d, $J=6.4$ Hz, 3H), 3.27 - 3.06 (m, 2H), 3.04 - 2.94 (m, 3H), 2.86 (br d, $J=3.5$ Hz, 1H), 2.76 (d, $J=4.6$ Hz, 3H), 2.20 - 1.56 (m, 8H), 1.09 - 1.01 (m, 3H), 0.73 - 0.23 (m, 4H) LPA1 $IC_{50} = 29$ nM	
263	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl((1-methylcyclopropyl)methyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS: $[M + H]^+ = 474.3$; 1H NMR (500 MHz, $DMSO-d_6$) δ 7.83 (br d, $J=8.5$ Hz, 1H), 7.46 (br d, $J=8.9$ Hz, 1H), 5.64 (br s, 2H), 4.77 (br s, 1H), 4.09 (s, 3H), 3.18 - 2.95 (m, 2H), 2.90 - 2.72 (m, 3H), 2.63 (br d, $J=10.4$ Hz, 1H), 2.40 (s, 3H), 2.05 - 1.40 (m, 8H), 0.97 - 0.66 (m, 3H), 0.43 - 0.07 (m, 4H) LPA1 $IC_{50} = 76$ nM	

Example	Structure & Name	Analytical & Biology Data	Method
264	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(neopentyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS: $[M + H]^+ = 474.4$; 1H NMR (500 MHz, DMSO-d_6) δ 7.84 (br s, 1H), 7.48 (br s, 1H), 5.63 (br d, $J=17.1$ Hz, 2H), 4.79 (br s, 1H), 4.11 (s, 3H), 3.57 (br dd, $J=12.1, 6.0$ Hz, 2H), 3.26 (dd, $J=10.4, 5.8$ Hz, 1H), 3.20 - 3.11 (m, 1H), 3.06 (br s, 1H), 2.93 (br s, 1H), 2.90 - 2.76 (m, 3H), 2.63 (br s, 1H), 2.09 - 1.43 (m, 8H), 0.92 - 0.64 (m, 9H) LPA1 $IC_{50} = 76$ nM	

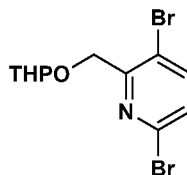
Example 265

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(hydroxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid

5



265A. 3,6-dibromo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine



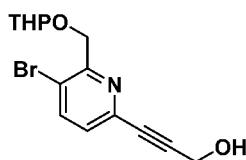
10

A solution of ethyl 3,6-dibromopicolinate (3.0 g, 9.71 mmol) in THF (50 mL) was stirred at 0 °C, then $LiBH_4$ (7.28 mL of a 2M solution in THF, 14.57 mmol) was added portionwise over 5 - 10 min. Vigorous gas evolution ensued. The reaction mixture

was stirred at rt overnight, then was quenched with 1N aq. HCl slowly, adjusting the pH to ~7. The mixture was partitioned between EtOAc and water (50 mL each) and extracted with EtOAc (3X). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (24 g SiO₂) to provide 3,6-dibromopyridin-2-yl)methanol (1.89 g, 7.08 mmol, 72.9 % yield).

To a solution of (3,6-dibromopyridin-2-yl)methanol (2.46 g, 9.22 mmol) in CH₂Cl₂ (12 mL) was added 3,4-dihydro-2H-pyran (2.52 mL, 27.6 mmol) and pyridinium p-toluenesulfonate (0.116 g, 0.461 mmol). The reaction was stirred overnight at rt, then quenched with water and extracted with DCM, washed with water, brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (24 g SiO₂, continuous gradient from 0-100% EtOAc/hexanes over 20 min) to give the title compound (3.4 g, 9.40 mmol, 100 % yield). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J=8.53 Hz, 1H), 7.32 (d, J=8.25 Hz, 1H), 4.94 (d, J=11.83 Hz, 1H), 4.88 (t, J=3.30 Hz, 1H), 4.69 (d, J=11.83 Hz, 1H), 3.94-4.09 (m, 1H), 3.49-3.70 (m, 1H), 1.49-2.00 (m, 8H)

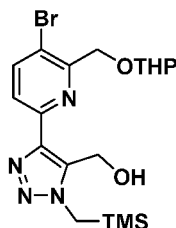
265B. 3-(5-Bromo-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-2-yl)prop-2-yn-1-ol



To a solution of Example 265A (3.4 g, 9.69 mmol) and prop-2-yn-1-ol (0.677 mL, 11.62 mmol) in MeCN (30 mL) was added Et₃N (6.00 mL). The solution was degassed with N₂ for 5 mins, after which Pd(Ph₃)₂Cl₂ (0.340 g, 0.484 mmol) and CuI (0.092 g, 0.484 mmol) were added. The reaction mixture was degassed with N₂ for 5 min, then was stirred at rt for 16 h under N₂. LCMS indicated at this time indicated that the reaction was complete. The reaction mixture was filtered through a pad of Celite and washed with EtOAc (4 x 30 mL). The filtrate was concentrated in vacuo and the residue was chromatographed (80 g SiO₂, elution by continuous gradient from 0% to 100% EtOAc/Hex over 80 min at 35 mL/min) to give the title compound (2.90 g, 8.89 mmol, 92 % yield). ¹H NMR (500 MHz, CDCl₃) δ 7.86 (d, J=8.25 Hz, 1H), 7.26 (d, J=8.25 Hz,

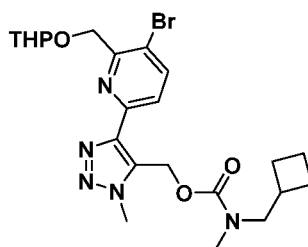
1H), 4.98 (d, J=11.55 Hz, 1H), 4.88 (t, J=3.30 Hz, 1H), 4.69 (d, J=11.55 Hz, 1H), 4.53 (d, J=6.05 Hz, 2H), 3.99 (dt, J=2.75, 10.45 Hz, 1H), 3.53-3.65 (m, 1H), 1.47-1.95 (m, 6H)

265C. (4-(5-Bromo-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-2-yl)-1-
5 (((trimethylsilyl)methyl)-1H-1,2,3-triazol-5-yl)methanol



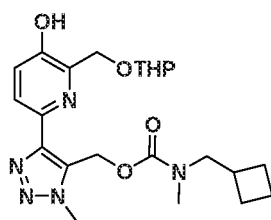
To a solution of Example 265B (2.9 g, 8.89 mmol) in dioxane (40 mL) was added
10 CuI (0.068 g, 0.356 mmol),
chloro(pentamethylcyclopentadienyl)bis(triphenylphosphine)Ruthenium(II) (0.283 g,
0.356 mmol). The resulting suspension was degassed with N₂ for 3 min, after which
trimethylsilylmethyl azide (1.404 g, 9.78 mmol) was added. The mixture was degassed
with N₂ for another 5 min, then was heated in an oil bath at 50°C for 20 h under N₂, then
15 was cooled to rt. The mixture was filtered through Celite; the filtrate was concentrated in
vacuo, and chromatographed (120 g SiO₂; elution with continuous gradient from 0 to 60%
EtOAc/Hex over 65 min at 120 mL/min) to give the title compound (2.30 g, 5.05 mmol,
56.8 % yield). ¹H NMR (500 MHz, CDCl₃) δ 8.10 (d, J=8.25 Hz, 1H), 7.97 (d, J=8.53 Hz,
1H), 6.41 (t, J=7.57 Hz, 1H), 5.05 (d, J=14.30 Hz, 1H), 4.86 (t, J=3.30 Hz, 1H), 4.80 (dd,
20 J=1.38, 7.43 Hz, 2H), 4.76 (d, J=14.03 Hz, 1H), 3.86-3.97 (m, 1H), 3.83 (s, 2H), 3.53-
3.64 (m, 1H), 1.51-2.02 (m, 8H), 0.18-0.27 (m, 9H)

265D. (4-(5-Bromo-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-2-yl)-1-methyl-
1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate
25



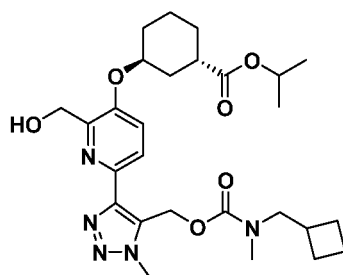
TBAF (5.56 mL of a 1M solution in THF, 5.56 mmol) was added dropwise to a solution of Example 265C (2.3 g, 5.05 mmol) in THF (15 mL) and the reaction mixture was stirred at rt overnight, then was quenched with sat'd aq. NaHCO₃ (50 mL) and stirred for 20 min at rt. The mixture was extracted with EtOAc (2 x 100 mL); the combined organic extracts were dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was chromatographed (40 g SiO₂; continuous gradient from 0% to 100% EtOAc over 30 min, at 20 mL/min) to give 4-(5-bromo-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methanol (1.69 g, 4.41 mmol, 87 % yield). To a solution of this material (0.41 g, 1.07 mmol) and pyridine (0.433 mL, 5.35 mmol) in DCM (5 mL) was added 4-nitrophenyl chloroformate (0.431 g, 2.140 mmol) in DCM (2 mL). The reaction mixture was stirred at rt overnight, then (cyclobutylmethyl)methylamine (0.318 g, 3.21 mmol) was added, followed by Et₃N (1.49 mL, 10.7 mmol). The reaction was stirred at rt for 3 h, then was partitioned between DCM and sat'd aq. NaHCO₃. The organic layer was washed with brine and concentrated in vacuo. The residue was chromatographed (40 g SiO₂; continuous gradient from 0% to 100% EtOAc over 30 min, at 20ml/min) to give the title compound (0.52 g, 0.921 mmol, 86 % yield). ¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, J=8.3 Hz, 1H), 7.96 (d, J=8.3 Hz, 1H), 5.83 (br d, J=16.0 Hz, 2H), 5.01 (d, J=11.8 Hz, 1H), 4.93 (t, J=3.2 Hz, 1H), 4.77 (d, J=12.1 Hz, 1H), 4.10-4.24 (m, 3H), 3.90-4.07 (m, 1H), 3.53-3.70 (m, 1H), 3.10-3.42 (m, 2H), 2.70-2.98 (m, 3H), 1.46-2.05 (m, 13H).

265E. 4-(5-hydroxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)methyl (cyclobutylmethyl)(methyl)carbamate



To a degassed solution of Example 265D (510 mg, 1.00 mmol), 4,4',4',5,5,5',5'-
 octamethyl-2,2'-bi(1,3,2-dioxaborolane) (509 mg, 2.01 mmol) and KOAc (295 mg, 3.01
 5 mmol) in THF (4013 μ l) was added PdCl₂(dppf) (36.7 mg, 0.050 mmol). The vial was
 purged with N₂, sealed and stirred at 80 °C overnight, then was cooled to rt. The mixture
 was diluted with EtOAc and filtered; the filtrate was concentrated in vacuo, re-dissolved
 in THF (5 mL) and this crude pinacol boronate product was used in the next step without
 further purification. To the solution of this crude pinacol boronate product in THF (5
 10 mL) was added aq. NaOH (2.01 mL of a 1 M solution, 2.01 mmol), followed by aq. H₂O₂
 (0.830 mL, 10.03 mmol). The reaction mixture was stirred at rt for 2 h, after which satd.
 aq. Na₂S₂O₃ (1 mL) was added; the mixture was stirred at rt for 10 min, then was
 extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄)
 and concentrated in vacuo. The residue was chromatographed (24 g SiO₂; continuous
 15 gradient from 0 to 100% EtOAc/Hex over 20 min at 20 mL/min) to give the title
 compound (379 mg, 0.851 mmol, 85 % yield). ¹H NMR (500 MHz, CDCl₃) δ 8.22 (br s,
 1H), 8.07 (d, J=8.53 Hz, 1H), 7.30 (d, J=8.53 Hz, 1H), 5.73 (br d, J=9.08 Hz, 2H), 5.14
 (d, J=12.93 Hz, 1H), 4.92 (d, J=12.65 Hz, 1H), 4.77-4.86 (m, 1H), 4.15 (br d, J=5.23 Hz,
 3H), 3.96-4.06 (m, 1H), 3.60-3.73 (m, 1H), 3.34 (br d, J=7.43 Hz, 1H), 3.18 (br d, J=6.88
 20 Hz, 1H), 2.74-2.99 (m, 3H), 1.60-1.98 (m, 13H)

265E. Isopropyl (1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-
 1-methyl-1H-1,2,3-triazol-4-yl)-2-(hydroxymethyl)pyridin-3-yl)oxy)cyclohexane-1-
 25 carboxylate



To a solution of Example 265D (275 mg, 0.617 mmol), Example 1F (610 mg, 1.54 mmol) in t-AmOH (5 mL) was added Cs₂CO₃ (603 mg, 1.85 mmol); the reaction
 5 was stirred at 65 °C for 24 h. Then more Example 1F (244 mg, 0.617 mmol) and Cs₂CO₃ (241 mg, 0.741 mmol) were added to the reaction, which was heated at 65 °C for another 24 h, then cooled to rt. Water (5 mL) was added and the mixture was stirred at rt for 10 min, then was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed (24 g SiO₂,
 10 continuous gradient from 0 to 100% EtOAc/Hex over 18 min at 15 mL/min) to give (1S,3S)-isopropyl 3-((6-(5-(((cyclobutylmethyl) (methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-3-yl)oxy)cyclohexanecarboxylate (290 mg, 0.402 mmol, 65.1 % yield).

A mixture of this THP ether (330 mg, 0.468 mmol) and PPTS (23.5 mg, 0.094
 15 mmol) in MeOH (4 mL) was heated at 60 °C overnight, then was cooled to rt. Volatiles were removed in vacuo and the residue was partitioned between DCM and satd aq. NaHCO₃. The organic extract was dried (Na₂SO₄) was concentrated in vacuo. The crude product was chromatographed (24 g SiO₂; continuous gradient from 0 to 100% EtOAc/Hex over 20 min at 20 mL/min and then at 100% EtOAc for 10 min) to give the
 20 title compound (274 mg, 0.491 mmol, 100 % yield). ¹H NMR (500 MHz, CDCl₃) δ 8.13 (br dd, J=3.71, 8.12 Hz, 1H), 7.32 (d, J=8.53 Hz, 1H), 5.70 (s, 2H), 4.99-5.14 (m, 1H), 4.78-4.90 (m, 1H), 4.75 (br s, 1H), 4.24 (s, 3H), 3.20-3.34 (m, 2H), 2.82-2.96 (m, 3H), 2.67-2.79 (m, 1H), 2.33-2.63 (m, 1H), 1.46-2.15 (m, 16H), 1.07-1.32 (m, 6H)

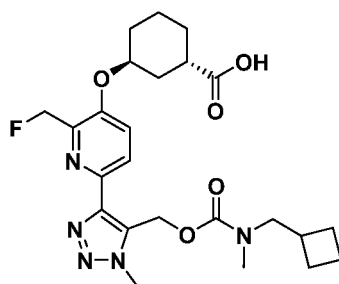
25 Example 265.

To a solution of 265E (17 mg, 0.032 mmol) in THF (0.5 mL) was added 4 drops of MeOH at rt, after which LiOH.H₂O (0.080 mL, 0.321 mmol) was added. The reaction

mixture was stirred at rt overnight, then was purified by preparative HPLC ((PHENOMENEX®, Axia 5 μ C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 0% B to 100%B over 10 min + 2 min hold time at 100% B, where A=90:10:0.1 H₂O:MeOH:TFA and B=90:10:0.1 MeOH:H₂O:TFA)) to give the title compound (15 mg, 0.024 mmol, 75 % yield). ¹H NMR (500 MHz, CDCl₃) δ 8.19 (br d, J=8.25 Hz, 1H), 7.65 (br d, J=8.53 Hz, 1H), 5.51-5.66 (m, 2H), 4.90-5.12 (m, 2H), 4.84 (br s, 1H), 4.24 (s, 3H), 3.29 (br dd, J=7.15, 16.78 Hz, 2H), 2.88 (br s, 4H), 2.38-2.68 (m, 1H), 1.49-2.22 (m, 15H). LCMS, [M+H]⁺ = 488.3. hLPA1 IC₅₀ = 68 nM

Example 266.

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(fluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



15

To a solution of Example 265E (50 mg, 0.094 mmol) in DCM (1 mL) at 0°C, was added bis(2-methoxyethyl)aminosulfur trifluoride (0.061 mL, 0.283 mmol) dropwise under N₂. The reaction mixture was gradually warmed to rt and stirred at rt for 2 h, then was slowly quenched by addition of satd aq. NaHCO₃ followed by DCM. The organic layer was dried using a stream of N₂ and the crude product (1S,3S)-isopropyl 3-((6-(5-(((cyclobutylmethyl)(methyl) carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(fluoromethyl)pyridin-3-yl)oxy) cyclohexanecarboxylate) was used in the next step without further purification. To a solution of the crude isopropyl ester (50 mg, 0.094 mmol) in THF (0.5 mL) was added 4 drops of MeOH at rt, followed by aq. LiOH (0.235 mL, 0.941 mmol). The reaction mixture was stirred at rt overnight, then was filtered. The crude product was purified by preparative HPLC (PHENOMENEX®, Axia 5 μ C18 30x100 mm column; detection at 220 nm; flow rate=40 mL/min; continuous gradient from 0% B to 100%B over 10 min+2 min hold time at 100% B, where A=90:10:0.1

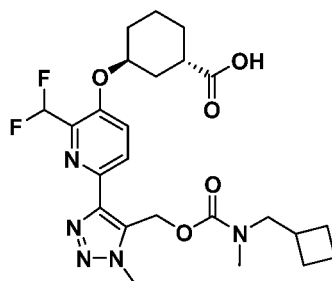
H₂O:MeOH:TFA and B=90:10:0.1 MeOH:H₂O:TFA to give the title compound (25 mg, 0.039 mmol, 41.8 % yield). ¹H NMR (500 MHz, CDCl₃) δ 8.19 (br d, J=8.53 Hz, 1H), 7.62-7.71 (m, 1H), 5.49-5.77 (m, 4H), 4.84 (br s, 1H), 4.22 (br d, J=4.40 Hz, 3H), 3.16-3.44 (m, 2H), 2.80-2.98 (m, 4H), 1.26-2.68 (m, 16H). LCMS, [M+H]⁺ = 490.3.

5 hLPA1 IC₅₀ = 27 nM.

Example 267.

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid

10

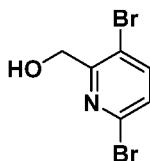


To a mixture of Example 265E (80 mg, 0.151 mmol) and 75 mg of Celite in DCM (1.5 mL) was added pyridinium dichromate (73.9 mg, 0.196 mmol). The reaction mixture was stirred at rt for 90 min, after which more pyridinium dichromate (73.9 mg, 0.196 mmol) was added, and the reaction was stirred overnight at rt. EtOAc was added and the mixture was filtered through Celite. The filtrate was concentrated in vacuo, and the crude product was chromatographed (4 g SiO₂, continuous gradient from 0 to 100% EtOAc/Hex over 12 min at 8 mL/min) to give (1S,3S)-isopropyl 3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-formylpyridin-3-yl)oxy)cyclohexanecarboxylate (15 mg, 0.028 mmol, 18 % yield). To a RT solution of the above aldehyde (15 mg, 0.028 mmol) in DCM (0.3 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (0.032 mL, 0.148 mmol) in one portion. The mixture was stirred at rt for 2h; volatiles were removed via an N₂ stream, and the crude difluoromethyl product (1S,3S)-isopropyl 3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexanecarboxylate was directly in the next step without further purification. To a solution of this isopropyl ester (13 mg, 0.024 mmol) in THF (0.5 mL) was added aq.

LiOH (0.118 mL, 0.473 mmol) and 4 drops of MeOH. The reaction mixture was stirred at rt for 2 days, filtered and the crude product was purified by preparative HPLC, (PHENOMENEX®, Axia 5 μ C18 30x100 mm column; detection at 220 nm; flow rate=40 mL/min; continuous gradient from 0% B to 100%B over 10 min+2 min hold time at 100% B, where A=90:10:0.1 H₂O:MeOH:TFA and B=90:10:0.1 MeOH:H₂O:TFA) to give the title compound (2 mg, 3.19 μ mol, 13.5 % yield). ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J=8.80 Hz, 1H), 7.37-7.65 (m, 1H), 6.62-7.05 (m, 1H), 5.71 (br s, 2H), 4.80 (br d, J=2.64 Hz, 1H), 4.17 (br d, J=7.92 Hz, 3H), 3.09-3.45 (m, 2H), 2.72-3.02 (m, 4H), 1.36-2.65 (m, 15H). LCMS, [M+H]⁺ = 508.2. hLPA IC₅₀ = 30 nM

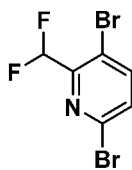
Alternatively, the title compound can also be synthesized as follows.

267A. (3,6-Dibromopyridin-2-yl)methanol



To a 0 °C solution of ethyl 3,6-dibromopicolinate (5.0 g, 16.2 mmol) in THF (30 mL) was added LiBH₄ in THF (12.14 mL of a 2 M solution, 24.28 mmol) portionwise over 10 min. Vigorous gas evolution ensued. After 1 h at rt, the reaction mixture was slowly quenched with satd aq., stirred for 10 min, then was extracted with EtOAc. The pH of the aqueous phase was adjusted to 7-8 by addition of 1N aq. HCl, then was extracted again with EtOAc. The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude material was chromatographed (40 g SiO₂; EtOAc/Hexane; continuous gradient from 0% to 100% EtOAc over 30 min, at 20 mL/min) to give the title compound (3.0 g, 11.24 mmol, 69.4 % yield), ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J=7.98 Hz, 1H), 7.35 (d, J=7.98 Hz, 1H), 4.77 (d, J=4.95 Hz, 2H), 3.78 (t, J=5.09 Hz, 1H)

267B. 3,6-Dibromo-2-(difluoromethyl)pyridine



Anhydrous DMSO (4.04 mL, 56.9 mmol) was added dropwise to a solution of (COCl)₂ (2.277 mL, 26.0 mmol) in DCM (25 mL) at -78°C. After stirring at -78°C for 5 15 min, a solution of Example 267A (2.17 g, 8.13 mmol) in DCM (25 mL) was added dropwise. After stirring for 15 min at -78°C, TEA (10.2 mL, 73.2 mmol) was added dropwise. The reaction was allowed to warm to rt over 1 h (the reaction mixture became cloudy); more DCM (50 mL) was added and the mixture was stirred for 2h at rt. The reaction was quenched with brine (20 mL) and extracted with DCM (2 x 50 mL). The 10 combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude oil was chromatographed (80 g SiO₂; elution with EtOAc/Hexane (continuous gradient from 0% to 60% over 20 min) to give 3,6-dibromopicolinic aldehyde (1.92 g, 7.25 mmol, 89 % yield) as a light yellowish oil. To a solution of the 3,6-dibromopicolinic aldehyde (1.5 g, 5.66 mmol) in DCM (6 mL) at rt was added bis(2-methoxyethyl)aminosulfur trifluoride 15 (1.46 mL, 6.79 mmol) in one portion. The mixture was stirred at rt for 1 h, then was carefully quenched with sat'd aq. NaHCO₃, adjusted to pH=7-8 and extracted with DCM (2X). The combined organic extracts were concentrated in vacuo. The residue was chromatographed (EtOAc/Hexane; continuous gradient from 0% to 100% EtOAc over 20 min, at 15 mL/min) to give the title compound (1.48 g, 5.16 mmol, 91 % yield). ¹H NMR 20 (500 MHz, CDCl₃) δ 7.83 (d, J=8.53 Hz, 1H), 7.51 (d, J=8.53 Hz, 1H), 6.65-7.00 (m, 1H)

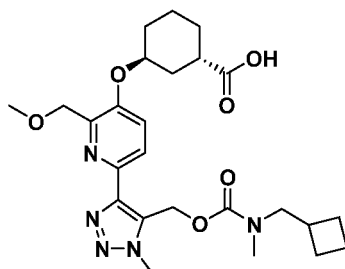
Example 267B can then be used as the starting material for the synthesis of Example 267. The synthetic sequence is analogous to that used for the synthesis of Example 1 (i.e. regioselective Sonogashira coupling of the less hindered bromide of Example 267B with propargyl alcohol, followed by Ru-mediated [3+2] cycloaddition 25 with trimethylsilyl azide to form the 1,2,3-triazole, etc.).

Example 267: ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J=8.80 Hz, 1H), 7.37-7.65 (m, 1H), 6.62-7.05 (m, 1H), 5.71 (br s, 2H), 4.80 (br d, J=2.64 Hz, 1H), 4.17 (br d, J=7.92 Hz, 3H), 3.09-3.45 (m, 2H), 2.72-3.02 (m, 4H), 1.36-2.65 (m, 15H). LCMS, [M+H]⁺ = 508.2 hLPA1 IC₅₀ = 30 nM

30

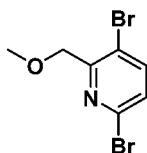
Example 268.

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



5

268A. 3,6-Dibromo-2-(methoxymethyl)pyridine



10 A solution of (3,6-dibromopyridin-2-yl)methanol (1.67 g, 6.26 mmol) in anhydrous THF (29 mL) was slowly added to a stirring suspension of NaH (0.30 g, 7.51 mmol) in anhydrous THF (5 mL) at 0-5°C under N₂. After gas evolution stopped, MeI (0.587 mL, 9.38 mmol) was added slowly dropwise and the reaction was warmed to rt over 1 h. Brine (10 mL) was added slowly to the reaction, which was then extracted with

15 EtOAc (2 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude material was chromatographed (24 g SiO₂; EtOAc/Hexane; continuous gradient from 0% to 100% EtOAc over 30 min, at 10 mL/min) to give the title compound (1.70 g, 6.05 mmol, 97 % yield). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J=8.25 Hz, 1H), 7.34 (d, J=8.25 Hz, 1H), 4.66 (s, 2H), 3.52 (s, 3H).

20

Example 268B was then used for the synthesis of Example 268. The synthetic sequence is analogous to that used for the synthesis of Example 1 (i.e. regioselective Sonogashira coupling of the less hindered bromide of Example 268B with propargyl alcohol, followed by Ru-mediated [3+2] cycloaddition with trimethylsilyl azide to form

25 the 1,2,3-triazole, etc.).

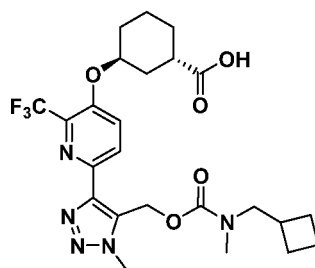
Example 268: ^1H NMR (500 MHz, DMSO- d_6) δ 7.95 (br d, $J=8.24$ Hz, 1H), 7.60 (br d, $J=8.85$ Hz, 1H), 5.63 (br d, $J=12.82$ Hz, 2H), 4.81 (br s, 1H), 4.53 (br s, 2H), 4.10 (br s, 3H), 3.03-3.27 (m, 2H), 2.68-2.82 (m, 3H), 2.59 (br d, $J=10.38$ Hz, 1H), 2.56 (s, 3H), 1.32-2.36 (m, 16H); LCMS, $[\text{M}+\text{H}]^+ = 502.3$; hLPA1 $\text{IC}_{50} = 103$ nM

5

Example 269.

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid

10



Example 269 was synthesized using commercially available 3,6-dibromo-2-(trifluoromethyl) pyridine, using the same synthetic sequence as for the preparation of Example 1.

15

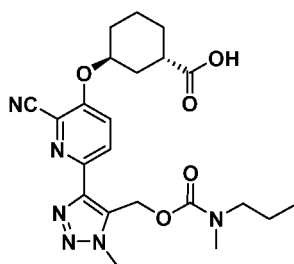
Example 269: ^1H NMR (500 MHz, CDCl_3) δ 8.39 (br d, $J=8.80$ Hz, 1H), 7.54 (d, $J=9.08$ Hz, 1H), 5.71 (br s, 1H), 4.86 (br s, 1H), 4.21 (br d, $J=13.76$ Hz, 3H), 3.12-3.40 (m, 2H), 2.89-2.99 (m, 1H), 2.74-2.89 (m, 3H), 2.35-2.66 (m, 1H), 2.17-2.37 (m, 1H), 1.42-2.29 (m, 14H)

20 LCMS, $[\text{M}+\text{H}]^+ = 526.2$; hLPA1 $\text{IC}_{50} = 10$ nM.

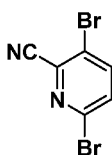
Example 270.

(1S,3S)-3-((2-cyano-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid

25



270A. 3,6-Dibromopicolinonitrile



5

To a suspension of 3,6-dibromopicolinic acid (0.5 g, 1.780 mmol), NH₄Cl (0.381 g, 7.12 mmol) and Et₃N (1.985 ml, 14.24 mmol) in THF (7.12 mL) was added 1-propanephosphonic anhydride (4.24 mL, 7.12 mmol) dropwise at 0 °C. The reaction was slowly warmed to rt, then was heated to 80 °C for 48 h, then was cooled to rt. The mixture was partitioned between water and EtOAc (10 mL each) and extracted with EA (2 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed (40 g SiO₂; EtOAc/Hexane; continuous gradient from 0% to 100% EtOAc over 30 min, at 20 mL/min) to give the title compound (0.32 g, 1.22 mmol, 68.6 % yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, J=8.53 Hz, 1H), 7.60 (d, J=8.53 Hz, 1H).

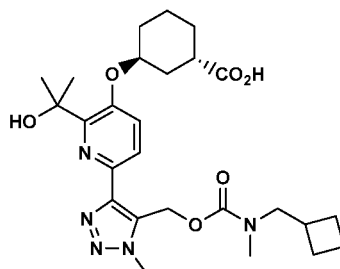
Example 270 was synthesized using Example 270A, using the same synthetic sequence as for the preparation of Example 1 (except that N-methyl, N-propylamine was used to generate the carbamate of Example 270 rather than the N-methyl, N-cyclobutylmethylamine that was used in Example 1).

Example 270: ¹H NMR (500 MHz, DMSO-d₆) δ 8.30 (d, J=9.16 Hz, 1H), 7.98 (d, J=9.16 Hz, 1H), 5.54 (br d, J=19.53 Hz, 2H), 5.01 (br s, 1H), 4.14 (s, 3H), 3.00-3.25 (m, 2H), 2.77 (br d, J=9.16 Hz, 3H), 2.63 (br t, J=10.22 Hz, 1H), 1.15-2.21 (m, 10H), 0.58-0.96 (m, 3H)

LCMS, [M+H]⁺ = 457.1; hLPA1 IC₅₀ = 11 nM

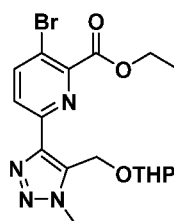
Example 271.

(1S,3S)-3-((6-(5-(((cyclobutylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(2-hydroxypropan-2-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid



5

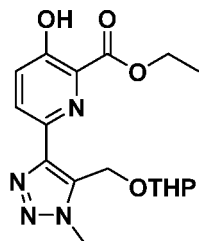
271A. Ethyl 3-bromo-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)picolinate



10 This compound was synthesized from commercially available ethyl 3,6-dibromopicolinate, using the same synthetic sequence as for Example 265. ¹H NMR (500 MHz, CDCl₃) δ 8.20 (d, J=8.53 Hz, 1H), 8.05 (d, J=8.53 Hz, 1H), 5.26-5.40 (m, 2H), 4.76 (t, J=3.44 Hz, 1H), 4.50 (q, J=7.15 Hz, 2H), 4.19 (s, 3H), 3.83 (ddd, J=3.03, 8.05, 11.21 Hz, 1H), 3.46-3.62 (m, 1H), 1.51-1.88 (m, 6H), 1.48 (t, J=7.15 Hz, 3H)

15

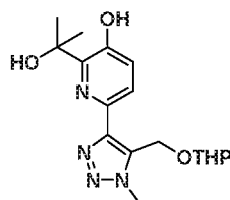
271B. Ethyl 3-hydroxy-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)picolinate



To a degassed solution of Example 271A (433 mg, 1.02 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (517 mg, 2.036 mmol) and KOAc (300 mg, 3.05 mmol) in THF (4.07 mL) was added PdCl₂(dppf) (37.2 mg, 0.051 mmol). The vial was purged with N₂, sealed and stirred at 80 °C overnight, then was cooled to rt. The mixture was filtered and the filtrate (crude pinacol boronate) was used directly in the next step without further purification

To a solution of the above crude boronate product (397 mg, 1.018 mmol) in EtOAc (7 mL) and THF (2 mL) was added H₂O₂ (0.946 mL, 10.2 mmol). The reaction was stirred at rt for 3 h, then was extracted with EtOAc. To the aqueous phase was added satd aq. Na₂S₂O₃ (3 mL) and 2 drops of 1N aq. NaOH; the mixture was stirred for 5 min and extracted again with EtOAc (2 X 5 mL). The combined organic extracts were concentrated in vacuo. The residue was chromatographed (40 g SiO₂; EtOAc/Hexane - continuous gradient from 0% to 100% EtOAc over 30 min, at 20 mL/min) to give the title compound (328 mg, 88 % yield). ¹H NMR (500 MHz, CDCl₃) δ 10.74 (s, 1H), 8.35 (d, J=8.80 Hz, 1H), 7.46 (d, J=8.80 Hz, 1H), 5.22-5.57 (m, 2H), 4.81 (t, J=3.58 Hz, 1H), 4.52 (dq, J=2.06, 7.11 Hz, 2H), 4.19 (s, 3H), 3.93 (br s, 1H), 3.84 (ddd, J=2.61, 8.32, 11.07 Hz, 1H), 3.43-3.60 (m, 1H), 1.48-2.06 (m, 9H)

271C. 2-(2-hydroxypropan-2-yl)-6-(1-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-ol



To a solution of Example 271B (0.3g, 0.828 mmol) in THF (7 mL) was added dropwise CH₃MgBr (1.95 mL of a 3.5 M solution in THF, 6.62 mmol) at 0°C. The resulted mixture was allowed to warm to rt and stirred at rt for 3 h. Satd aq. NH₄Cl was then carefully added to quench the reaction, which was extracted with EtOAc. The aqueous layer was carefully adjusted to pH 6 by using 1 N aq. HCl, then extracted again with EtOAc (2X). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude product was chromatographed (24 g SiO₂; EtOAc/Hexane -

continuous gradient from 0% to 100% EtOAc over 30 min, at 10 mL/min) to give the title compound (110 mg, 0.316 mmol, 38.1 % yield).

Example 271.

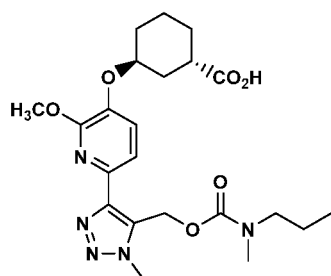
- 5 Example 271C was converted to Example 271 by a similar sequence used to convert Example 1C to Example 1.

¹H NMR (500 MHz, DMSO-d₆) δ 7.96 (d, J=8.54 Hz, 1H), 7.59 (br d, J=8.54 Hz, 1H), 5.49 (s, 2H), 4.85 (br s, 1H), 4.13 (br s, 2H), 3.79 (br d, J=16.78 Hz, 1H), 3.07-3.26 (m, 2H), 2.88 (s, 1H), 2.68-2.75 (m, 2H), 2.55 (s, 3H), 1.19-2.16 (m, 20H). LCMS, [M+H]⁺
10 = 516.3.

hLPA₁ IC₅₀ = 225 nM

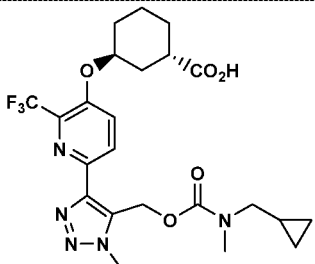
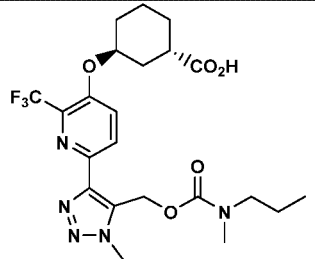
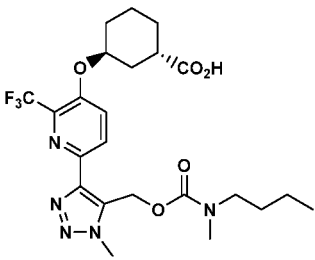
Example 272.

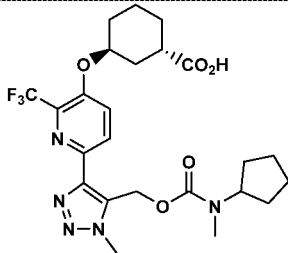
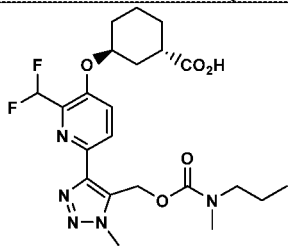
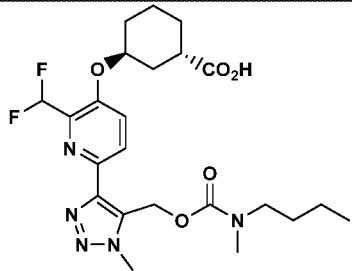
- (1S,3S)-3-((2-Methoxy-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-
15 1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid

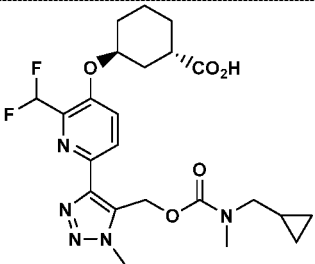
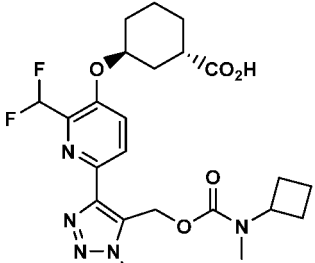
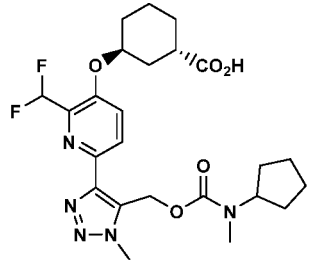


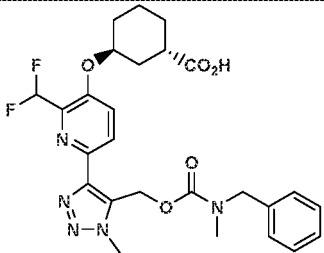
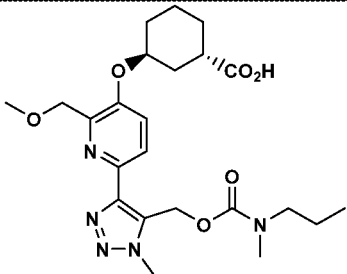
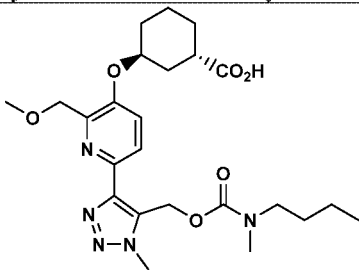
- Example 272 was synthesized from 3,6-dibromo-2-(methoxy)pyridine using the
20 same synthetic sequence as for the preparation of Example 1 from 3,6-dibromopyridine.
LCMS, [M+H]⁺ = 462.1; ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, J=8.0 Hz, 1H), 7.33 -
7.30 (m, 1H), 5.79 (br s, 2H), 4.72 - 4.67 (m, 1H), 4.18 (s, 3H), 4.04 (s, 3H), 3.25 (br t,
J=7.3 Hz, 1H), 3.18 - 3.07 (m, 1H), 3.06 - 2.95 (m, 1H), 2.92 (s, 1.5H), 2.83 (s, 1.5H),
2.16 - 2.07 (m, 2H), 2.05 - 1.83 (m, 4H), 1.79 - 1.68 (m, 2H), 1.68 - 1.52 (m, 2H), 1.50 -
25 1.33 (m, 1H), 0.95 - 0.85 (m, 1.5H), 0.76 (br t, J=7.2 Hz, 1.5H)
hLPA₁ IC₅₀ = 4 nM

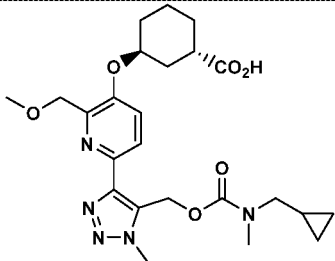
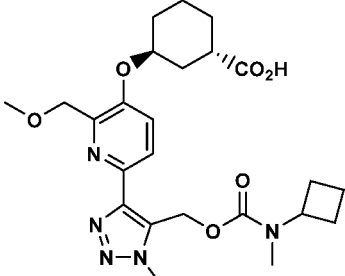
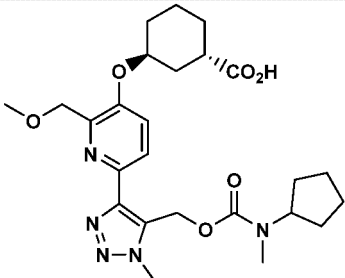
The following examples were synthesized according to the procedures described above.

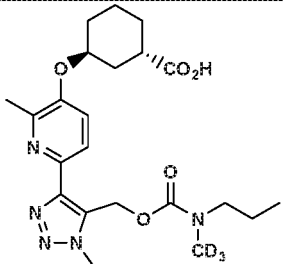
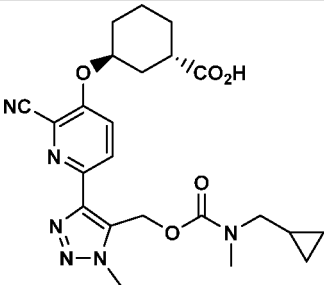
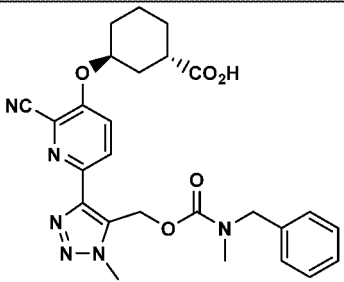
Example	Structure & Name	Analytical & Biology Data	Method
273	 (1S,3S)-3-((6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	LCMS, [M+H]⁺ = 512.4 ¹H NMR (500 MHz, DMSO-d₆) δ 8.33 (br d, J=8.85 Hz, 1H), 7.87-8.11 (m, 1H), 5.62 (br d, J=17.09 Hz, 2H), 5.06 (br s, 1H), 4.18 (s, 2H), 2.69-3.38 (m, 6H), 2.11 (br d, J=13.43 Hz, 1H), 1.78-2.02 (m, 3H), 1.44-1.76 (m, 3H), 1.14-1.35 (m, 1H), 1.05 (d, J=6.10 Hz, 1H), 0.71-0.97 (m, 1H), 0.47 (br s, 1H), 0.30 (br s, 2H), 0.13-0.26 (m, 1H) hLPA1 IC₅₀ = 7 nM.	Example 269
274	 (1S,3S)-3-((6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.27 (br d, J=8.54 Hz, 1H), 7.95 (br d, J=8.85 Hz, 1H), 5.57 (br d, J=13.43 Hz, 2H), 5.01 (br s, 1H), 4.13 (s, 2H), 2.97-3.21 (m, 2H), 2.93 (q, J=7.22 Hz, 2H), 2.65-2.79 (m, 3H), 1.21-2.13 (m, 8H), 1.17 (t, J=7.17 Hz, 3H), 0.50-0.85 (m, 2H) LCMS, [M+H]⁺ = 499.9 hLPA1 IC₅₀ = 28 nM.	Example 269
275	 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.27 (br d, J=8.85 Hz, 1H), 7.94 (br d, J=8.85 Hz, 1H), 5.55 (br d, J=12.82 Hz, 2H), 5.00 (br s, 1H), 4.13 (br s, 3H), 2.99-3.23 (m, 2H), 2.92 (q, J=7.32 Hz, 1H), 2.74 (br s, 1H), 2.70 (br s, 2H), 1.33-2.13 (m, 10H), 1.08-1.27 (m, 3H), 0.91-1.00 (m, 1H), 0.85 (br s, 1H), 0.61 (br s, 2H) LCMS, [M+H]⁺ = 514.1 hLPA1 IC₅₀ = 5.6 nM.	Example 269

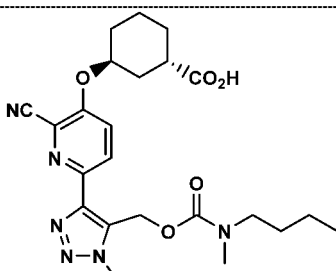
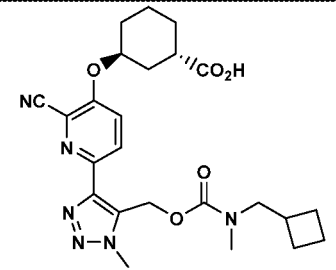
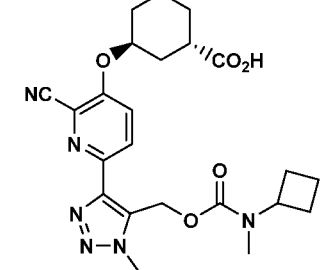
Example	Structure & Name	Analytical & Biology Data	Method
276	 (1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.27 (d, J=8.84 Hz, 1H), 7.96 (d, J=9.00 Hz, 1H), 5.56 (br s, 2H), 5.01 (br s, 1H), 4.13 (s, 3H), 3.65 (m, 1H), 2.54-2.70 (m, 4H), 1.73-2.14 (m, 4H), 1.25-1.71 (m, 12H) LCMS, [M+H]⁺ = 526.5 hLPA1 IC₅₀ = 15 nM.	Example 269
277	 (1S,3S)-3-((2-(difluoromethyl)-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.16 (br d, J=8.24 Hz, 1H), 7.82 (br d, J=8.85 Hz, 1H), 7.01-7.34 (m, 1H), 5.62 (br d, J=13.12 Hz, 2H), 4.94 (br s, 1H), 4.13 (s, 3H), 2.95-3.22 (m, 2H), 2.75 (br d, J=16.78 Hz, 3H), 2.66 (br t, J=10.68 Hz, 1H), 2.06 (br d, J=13.43 Hz, 1H), 1.39-1.95 (m, 8H), 1.18-1.34 (m, 2H), 0.52-0.88 (m, 3H) LCMS, [M+H]⁺ = 482.2 hLPA1 IC₅₀ = 35 nM	Example 267
278	 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.16 (d, J=8.85 Hz, 1H), 7.82 (br d, J=8.85 Hz, 1H), 6.87-7.22 (m, 1H), 5.62 (br d, J=10.99 Hz, 2H), 4.93 (br s, 1H), 4.13 (br s, 3H), 2.96-3.29 (m, 2H), 2.61-2.87 (m, 4H), 0.52-2.18 (m, 15H) LCMS, [M+H]⁺ = 496.2 hLPA1 IC₅₀ = 22 nM	Example 267

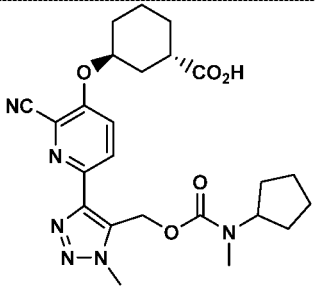
Example	Structure & Name	Analytical & Biology Data	Method
279	 (1S,3S)-3-((6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.16 (d, J=8.75 Hz, 1H), 7.80 (d, J=8.92 Hz, 1H), 6.84-7.23 (m, 1H), 5.63 (s, 2H), 4.92 (br s, 1H), 4.13 (s, 3H), 2.83 (s, 2H), 2.61-2.74 (m, 1H), 2.55 (s, 3H), 2.01-2.17 (m, 1H), 1.40-1.95 (m, 7H), 1.25 (s, 1H), -0.16-0.98 (m, 5H) LCMS, [M+H]⁺ = 494.2 hLPA1 IC₅₀ = 21 nM	Example 267
280	 (1S,3S)-3-((6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.16 (d, J=8.75 Hz, 1H), 7.80 (d, J=8.92 Hz, 1H), 6.89-7.22 (m, 1H), 5.62 (s, 2H), 4.92 (br s, 1H), 2.74 (s, 3H), 2.60-2.72 (m, 1H), 2.55 (s, 3H), 1.79 (d, J=123.19 Hz, 15H) LCMS, [M+H]⁺ = 494.2 hLPA1 IC₅₀ = 22 nM	Example 267
281	 (1S,3S)-3-((6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.16 (d, J=8.85 Hz, 1H), 7.82 (br d, J=8.85 Hz, 1H), 6.88-7.19 (m, 1H), 5.62 (br d, J=10.99 Hz, 2H), 4.93 (br s, 1H), 4.02-4.24 (m, 3H), 2.97-3.34 (m, 2H), 2.60-2.85 (m, 4H), -0.24-2.48 (m, 16H) LCMS, [M+H]⁺ = 508.2 hLPA1 IC₅₀ = 35 nM	Example 267

Example	Structure & Name	Analytical & Biology Data	Method
282	 (1S,3S)-3-((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.16 (br d, J=8.75 Hz, 1H), 7.80 (br d, J=8.84 Hz, 1H), 6.85-7.47 (m, 6H), 5.69 (br s, 2H), 4.91 (br s, 1H), 4.37 (br s, 2H), 4.07 (br d, J=14.22 Hz, 3H), 2.61-2.89 (m, 4H), 1.42-2.16 (m, 8H) LCMS, [M+H]⁺ = 530.9 hLPA1 IC₅₀ = 19 nM	Example 267
283	 (1S,3S)-3-((2-(methoxymethyl)-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 7.97 (br d, J=7.02 Hz, 1H), 7.61 (br d, J=8.54 Hz, 1H), 5.66 (br d, J=8.54 Hz, 2H), 4.84 (br s, 2H), 4.54 (br d, J=2.75 Hz, 2H), 4.11 (s, 3H), 3.34 (s, 1H), 2.97-3.22 (m, 2H), 2.71-2.86 (m, 3H), 2.62-2.70 (m, 1H), 1.23-2.13 (m, 10H), 1.01 (d, J=6.41 Hz, 1H), 0.56-0.87 (m, 3H) LCMS, [M+H]⁺ = 476.2 hLPA1 IC₅₀ = 475 nM	Example 268
284	 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 7.98 (br d, J=8.85 Hz, 1H), 7.61 (br d, J=8.85 Hz, 1H), 5.66 (br d, J=8.85 Hz, 2H), 4.84 (br s, 1H), 4.54 (d, J=2.44 Hz, 2H), 4.11 (s, 3H), 3.00-3.28 (m, 2H), 2.61-2.85 (m, 4H), 0.57-2.16 (m, 18H) LCMS, [M+H]⁺ = 490.3 hLPA1 IC₅₀ = 48 nM	Example 268

Example	Structure & Name	Analytical & Biology Data	Method
285	 (1S,3S)-3-(((6-(5-(((cyclopropyl methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 7.98 (br d, J=8.54 Hz, 1H), 7.60 (br d, J=8.54 Hz, 1H), 5.66 (br d, J=12.82 Hz, 2H), 4.82 (br s, 1H), 4.42-4.65 (m, 2H), 4.12 (s, 3H), 2.92-3.22 (m, 2H), 2.61-2.89 (m, 4H), 0.64-2.16 (m, 14H), -0.11-0.53 (m, 4H) LCMS, [M+H]⁺ = 488.3 hLPA1 IC₅₀ = 1008 nM	Example 268
286	 (1S,3S)-3-(((6-(5-(((cyclobutyl methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 7.96 (br d, J=8.54 Hz, 1H), 7.60 (br d, J=8.85 Hz, 1H), 5.63 (s, 2H), 4.82 (br s, 1H), 4.52 (br s, 2H), 4.09 (s, 3H), 3.32 (s, 3H), 2.59-2.81 (m, 4H), 1.26-2.24 (m, 15H) LCMS, [M+H]⁺ = 488.3 hLPA1 IC₅₀ = 92 nM	Example 268
287	 (1S,3S)-3-(((6-(5-(((cyclopentyl methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-(methoxymethyl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 7.98 (d, J=8.54 Hz, 1H), 7.61 (d, J=8.85 Hz, 1H), 5.66 (s, 2H), 4.84 (br s, 1H), 4.54 (d, J=2.75 Hz, 2H), 4.11 (s, 3H), 3.91 (s, 1H), 2.73-2.92 (m, 1H), 2.65 (br s, 3H), 2.56 (s, 1H), 1.24-2.12 (m, 17H) LCMS, [M+H]⁺ = 502.3 hLPA1 IC₅₀ = 118 nM	Example 268

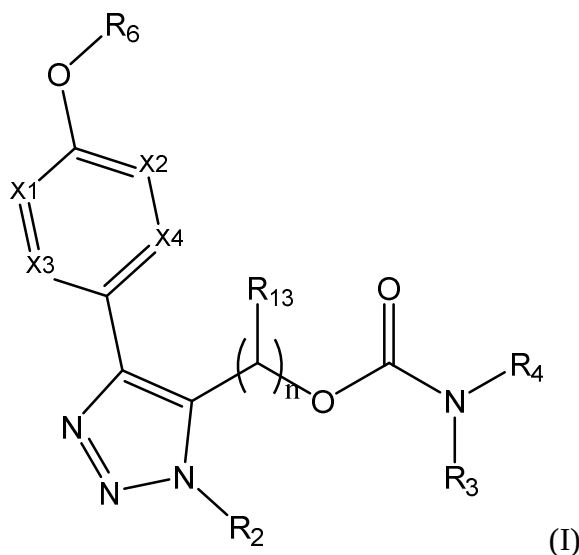
Example	Structure & Name	Analytical & Biology Data	Method
288	 (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl-d3)(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, CDCl₃) δ 8.12 (br d, J=8.53 Hz, 1H), 7.95 (br s, 1H), 5.39-5.59 (m, 2H), 4.87 (br s, 1H), 4.20 (br s, 3H), 3.23 (br s, 2H), 2.84 (br s, 1H), 2.68-2.79 (m, 3H), 1.46-2.19 (m, 10H), 0.88 (br s, 3H) LCMS, [M+H]⁺ = 449.1 hLPA1 IC₅₀ = 29 nM	Example 93
289	 (1S,3S)-3-((2-cyano-6-(5-(((cyclopropylmethyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.29 (d, J=8.85 Hz, 1H), 7.98 (br d, J=9.16 Hz, 1H), 5.45-5.65 (m, 2H), 4.99 (br s, 1H), 4.12 (s, 3H), 2.91-3.14 (m, 2H), 2.83 (br s, 3H), 2.56-2.69 (m, 1H), 1.41-2.04 (m, 8H), 0.71-1.03 (m, 1H), -0.08-0.50 (m, 4H) LCMS, [M+H]⁺ = 469.1 hLPA1 IC₅₀ = 40 nM	Example 270
290	 (1S,3S)-3-((6-(5-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-cyanopyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.30 (br s, 1H), 7.92 (br d, J=9.77 Hz, 1H), 6.91-7.38 (m, 5H), 5.47-5.72 (m, 2H), 5.00 (br s, 1H), 4.25-4.50 (m, 3H), 3.94-4.20 (m, 2H), 2.60-2.88 (m, 4H), 1.37-2.18 (m, 8H) LCMS, [M+H]⁺ = 505.3 hLPA1 IC₅₀ = 2 nM	Example 270

Example	Structure & Name	Analytical & Biology Data	Method
291	 (1S,3S)-3-((6-(5-(((butyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-cyanopyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.30 (br d, J=8.85 Hz, 1H), 7.98 (d, J=9.16 Hz, 1H), 5.40-5.65 (m, 2H), 5.00 (br s, 1H), 4.13 (br s, 3H), 2.99-3.29 (m, 2H), 2.70-2.83 (m, 3H), 2.62 (br t, J=9.92 Hz, 1H), 0.59-2.17 (m, 15H) LCMS, [M+H]⁺ = 471.3 hLPA1 IC₅₀ = 15 nM	Example 270
292	 (1S,3S)-3-((2-cyano-6-(5-(((cyclobutyl(methyl)(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.24-8.45 (m, 1H), 8.30 (br d, J=8.67 Hz, 1H), 7.97 (br d, J=9.09 Hz, 1H), 5.43-5.68 (m, 2H), 5.01 (br s, 1H), 4.05-4.22 (m, 3H), 3.56 (br s, 1H), 3.05-3.30 (m, 2H), 2.66-2.83 (m, 3H), 1.09-2.37 (m, 15H) LCMS, [M+H]⁺ = 483.2 hLPA1 IC₅₀ = 20 nM	Example 270
293	 (1S,3S)-3-((2-cyano-6-(5-(((cyclobutyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.30 (d, J=9.16 Hz, 1H), 7.97 (br d, J=9.16 Hz, 1H), 5.52 (br s, 2H), 5.00 (br s, 1H), 4.12 (s, 3H), 3.40-3.67 (m, 1H), 2.74 (br s, 3H), 2.57-2.66 (m, 1H), 1.29-2.22 (m, 14H) LCMS, [M+H]⁺ = 469.3 hLPA1 IC₅₀ = 23 nM	Example 270

Example	Structure & Name	Analytical & Biology Data	Method
294	 (1S,3S)-3-((2-cyano-6-(5-(((cyclopentyl(methyl)carbamoyl)oxy)methyl)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid	¹H NMR (500 MHz, DMSO-d₆) δ 8.29 (d, J=8.85 Hz, 1H), 7.97 (br d, J=9.16 Hz, 1H), 5.52 (br s, 2H), 5.00 (br s, 1H), 4.12 (s, 3H), 3.50-3.69 (m, 1H), 2.65 (br s, 3H), 2.60 (br s, 1H), 1.22-2.11 (m, 16H) LCMS, [M+H]⁺ = 483.3 hLPA1 IC₅₀ = 15 nM	Example 270

WHAT IS CLAIMED IS:

1. A compound according to Formula (I):



or stereoisomers, tautomers, a pharmaceutically acceptable salts, or solvates thereof, wherein

R₂ is independently selected from H and C₁₋₄ alkyl substituted with 1-5 R₉;

R₁₃ is independently selected from H, D, and C₁₋₄ alkyl substituted with 1-3 R₉;

- 10 R₃ and R₄ are independently selected from H, C₁₋₇ alkyl substituted with 1-3 R₉, - (CR₇R₇)_r-C₃₋₈ cycloalkyl substituted with 1-3 R₈, -(CR₇R₇)_r-aryl substituted with 1-3 R₈, C₂₋₇alkenyl substituted with 1-3 R₉, -(CR₇R₇)_r-5-6 membered heterocyclic ring substituted with 1-3 R₈, -(CR₇R₇)_r-5-6 membered heteroaryl ring substituted with 1-3 R₈, or R₃ and R₄ combine with the N to which they are attached to form a 4-9 membered heterocyclic ring substituted with 1-3 R₈;

X¹, X², X³, and X⁴ are independently selected from CR₅ and N; provided no more than two of X¹, X², X³, or X⁴ are N;

R₅ is independently selected from H, F, Cl, OR₇, CN, N(R₇)₂, C₁₋₄ alkyl substituted with 1-5 R₉, C₁₋₄ alkoxy substituted with 1-5 R₉, and C₁₋₄ heteroalkyl substituted with 1-5 R₉;

- 20 R₆ is C₃₋₈ cycloalkyl which is substituted with R₁₀ and (-CH₂)₀₋₁R₁₁;

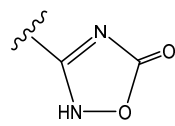
R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

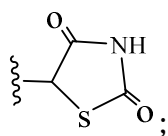
R₈ is independently selected from H, D, C₁₋₆ alkyl substituted with 1-5 R₉, C₂₋₆ alkenyl, C₂₋₆ alkynyl, phenyl, -(CH₂)_r-C₃₋₆ cycloalkyl, F, Cl, Br, CN, COOH, and C₁₋₄ alkoxy;

R₉ is independently selected from H, D, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₁₋₅ heteroalkyl C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not

5 substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H, D, C₁₋₄ alkyl, F, Cl, Br, OR₇, NHC(=O)OR₇, and NHC(=O)OR₇;

R₁₁ is independently selected from H, CN, -C(=O)R₁₂, tetrazolyl, , and



10 R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, NHCH₂CH₂SO₃H, and NHSO₂C₁₋₄alkyl;

r is independently selected from zero, 1, 2, 3, and 4,

and n is selected from 1, 2, 3, or 4.

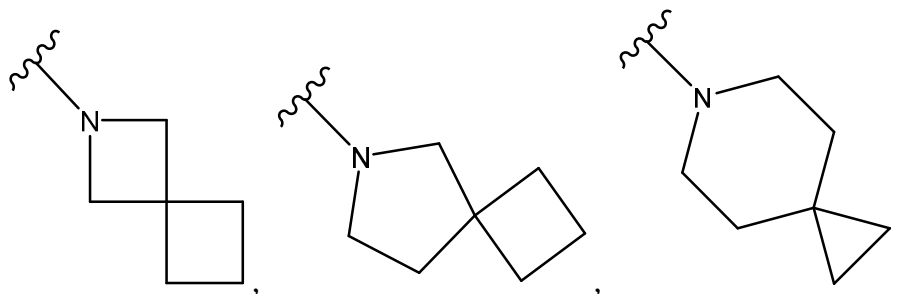
15 2. The compound of claim 1, wherein

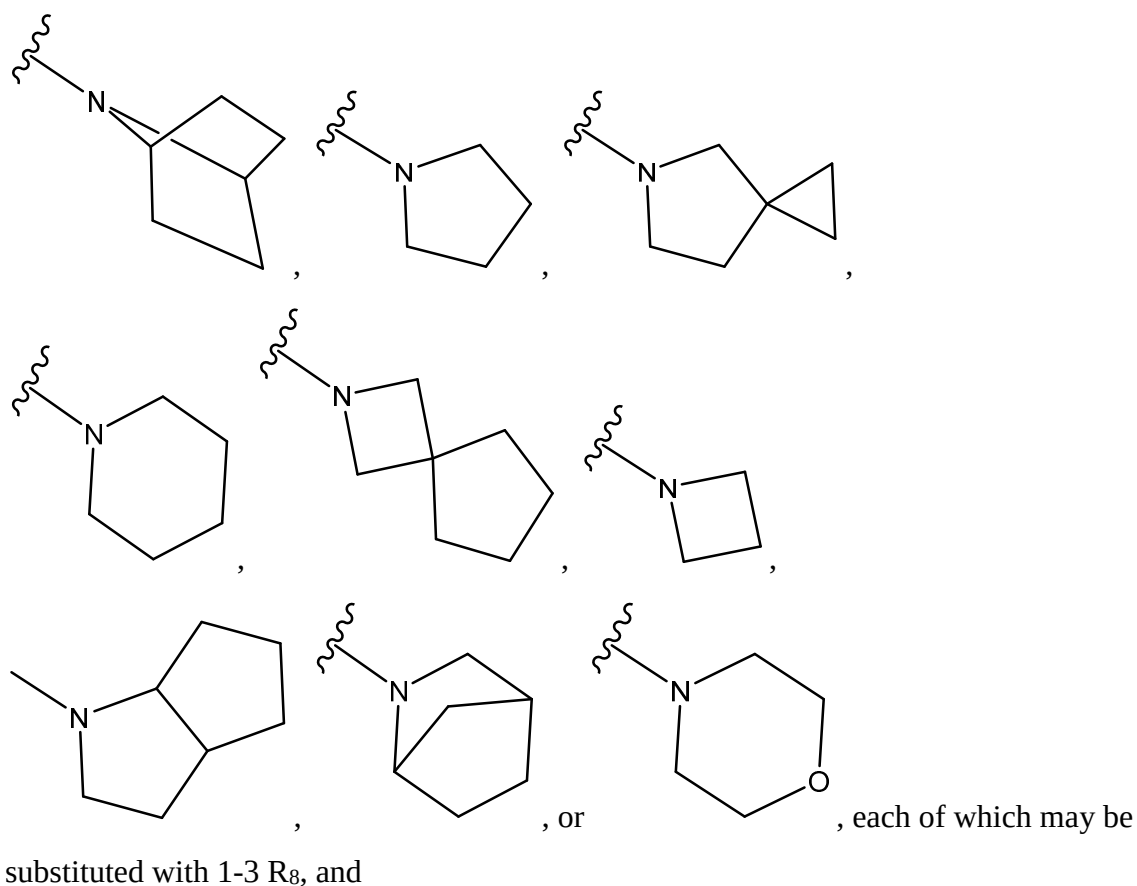
R₃ and R₄ are independently selected from H, C₁₋₇ alkyl substituted with 1-3 R₉, -

(CR₇R₇)_r-C₃₋₈ cycloalkyl substituted with 1-3 R₈, -(CR₇R₇)_r-aryl substituted with 1-3 R₈,

C₂₋₇alkenyl substituted with 1-3 R₉, -(CR₇R₇)_r-5-6 membered heterocyclic ring substituted with 1-3 R₈, -(CR₇R₇)_r-5-6 membered heteroaryl ring substituted with 1-3 R₈, and R₃ and

20 R₄ combine with the N to which they are attached to form the following:



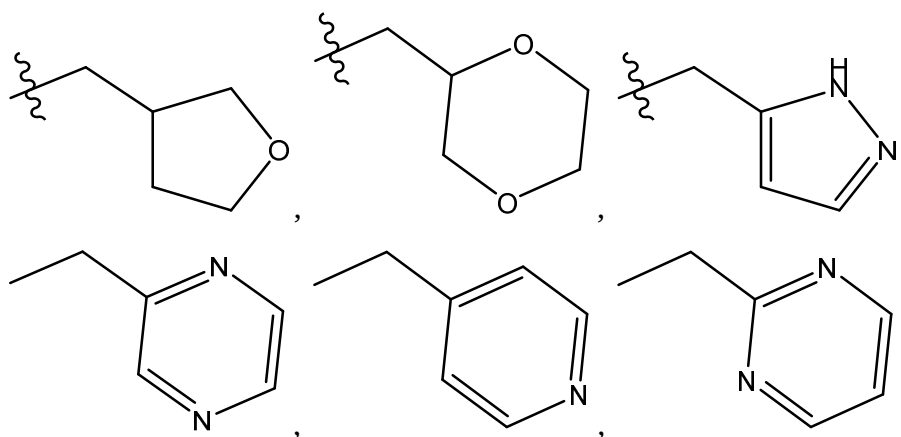


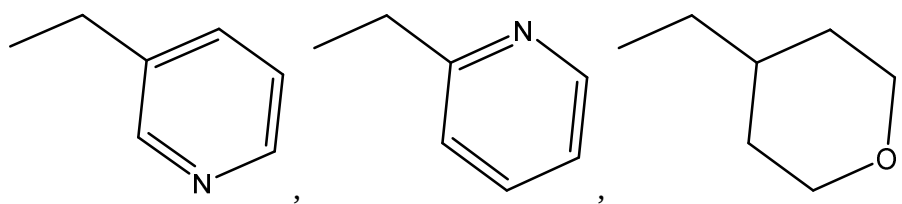
5 n equals 1 or 2.

3. The compound according to claim 1 wherein,

R_3 and R_4 are independently selected from H, C_{1-7} alkyl substituted with 1-3 R_9 , -
 $(CR_7R_7)_r$ - C_{3-8} cycloalkyl substituted with 1-3 R_8 , $-(CR_7R_7)_r$ -aryl substituted with 1-3
 R_8 , C_{2-7} alkenyl substituted with 1-3 R_9 ,

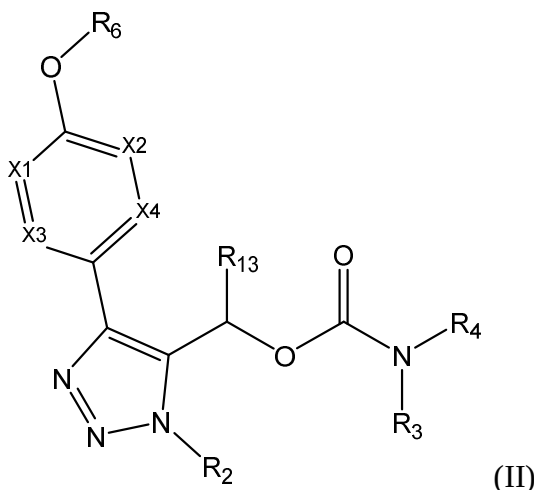
10





, each of which can be substituted with 1-3 R_8 , and R_3 and R_4 combine with the N to which they are attached to form a 4-9 membered heterocyclic ring substituted with 1-3 R_8 ; and
 n equals 1 or 2.

4. A compound according to claim 1 of Formula (II):



or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

R_2 is independently selected from H and C_{1-4} alkyl substituted with 1-5 R_9 ;

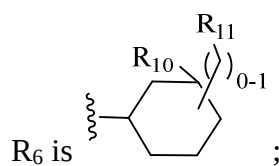
R_{13} is independently selected from H, D, and C_{1-4} alkyl substituted with 1-3 R_9 ;

R_3 and R_4 are independently selected from H, C_{1-7} alkyl substituted with 1-3 R_9 , -

(CR_7R_7) $_1$ - C_{3-6} cycloalkyl substituted with 1-3 R_8 , and -(CR_7R_7) $_1$ -aryl substituted with 1-3 R_8 ;

X^1 , X^2 , X^3 , and X^4 are independently selected from CR_5 and N; provided no more than two of X^1 , X^2 , X^3 , or X^4 are N;

R_5 is independently selected from H, F, Cl, OR_7 , CN, $N(R_7)_2$, C_{1-4} alkyl substituted with 1-5 R_9 , C_{1-4} alkoxy substituted with 1-5 R_9 , and C_{1-4} heteroalkyl substituted with 1-5 R_9 ;

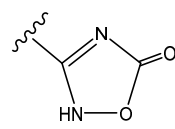


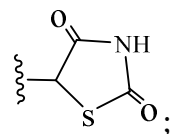
R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

- 5 R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_r-C₃₋₆ cycloalkyl, F, Cl, Br, CN, and COOH;

R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₁₋₅ heteroalkyl C₃₋₆ cycloalkyl, and phenyl wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

- 10 R₁₀ is independently selected from H, D, C₁₋₄ alkyl, F, Cl, Br, OR₇, NHC(=O)OR₇, and NHC(=O)OR₇;

R₁₁ is independently selected from CN, -C(=O)R₁₂, tetrazolyl, , and

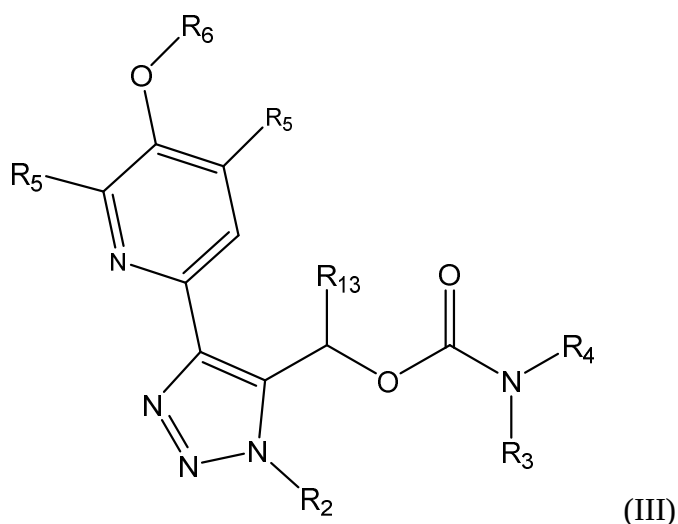


R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, NHCH₂CH₂SO₃H, and

- 15 NHSO₂C₁₋₄alkyl;

r is independently selected from zero, 1, 2, 3, and 4.

5. The compound of claim 4 having Formula (III):



or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

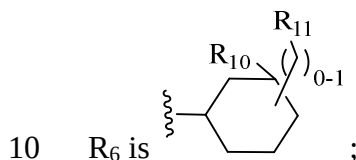
5 R₁₃ is independently selected from H and C₁₋₄ alkyl;

R₃ is independently selected from H and C₁₋₄ alkyl;

R₄ is independently selected from C₁₋₆ alkyl substituted with 1-3 R₉, -(CR₇R₇)_r-C₃₋₆

cycloalkyl substituted with 1-3 R₈, and -(CR₇R₇)_r-aryl substituted with 1-3 R₈;

R₅ is independently selected from H, F, Cl, CN and C₁₋₄ alkyl; provided one of R₅ is H;



R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and COOH;

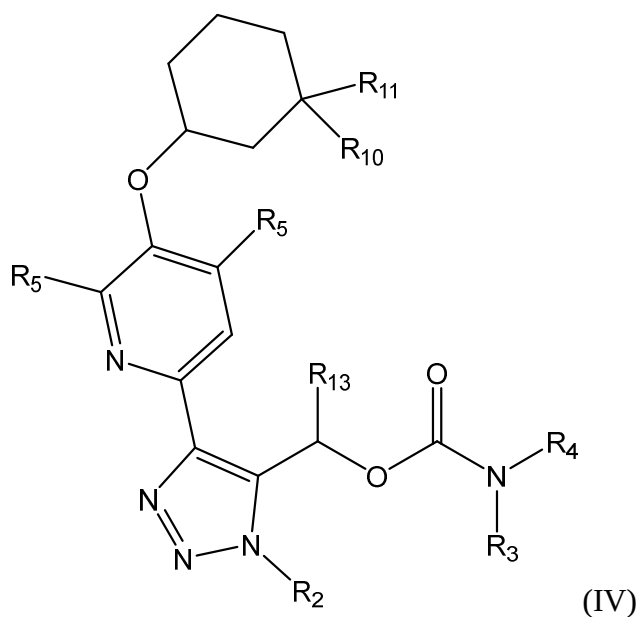
15 R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₃₋₆ cycloalkyl, and phenyl wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H, D, C₁₋₄ alkyl, and F;

R₁₁ is independently selected from CN, -C(=O)R₁₂, and tetrazolyl;

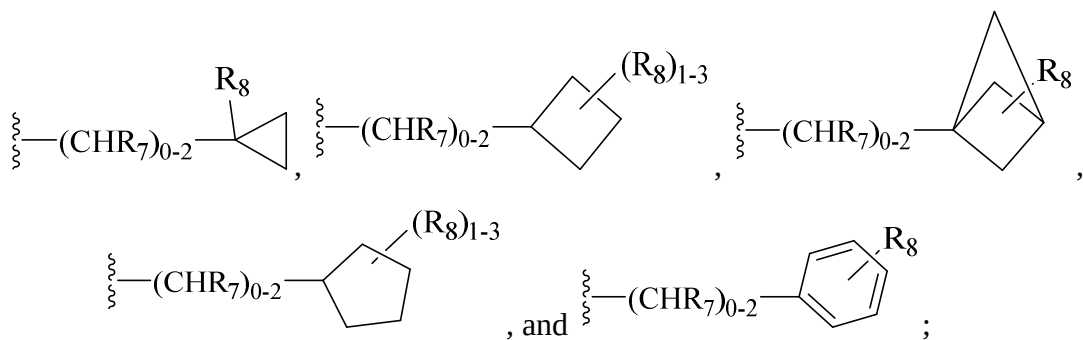
20 R₁₂ is independently selected from OH, OC₁₋₄ alkyl, NH₂, and NHSO₂C₁₋₄alkyl; and r is independently selected from zero, 1, 2, 3, and 4.

6. The compound of claim 5, having Formula (IV):



or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

- 5 R_2 is independently selected from CH_3 and CD_3 ;
 R_{13} is independently selected from H and C_{1-4} alkyl;
 R_3 is independently selected from H and C_{1-4} alkyl;
 R_4 is independently selected from C_{1-6} alkyl,

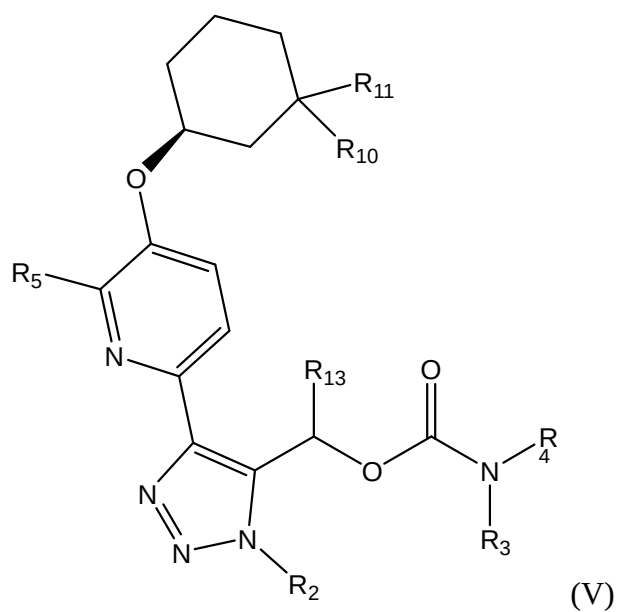


R_5 is independently selected from H, F, Cl, and C_{1-4} alkyl; provided one of R_5 is H;

R_7 is independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl;

R_8 is independently selected from H, C_{1-6} alkyl substituted with 1-5 R_9 , C_{3-6} cycloalkyl, F, Cl, Br, CN, =O, and COOH;

- 15 R_9 is independently selected from H, F, Cl, NH_2 , OH, OC_{1-5} alkyl, C_{1-5} alkyl, C_{3-6} cycloalkyl, and phenyl wherein when R_9 is Cl, NH_2 or OH it is not substituted on C_1 of the the alkyl to which it is attached;
 R_{10} is independently selected from H, D, C_{1-4} alkyl, and F;



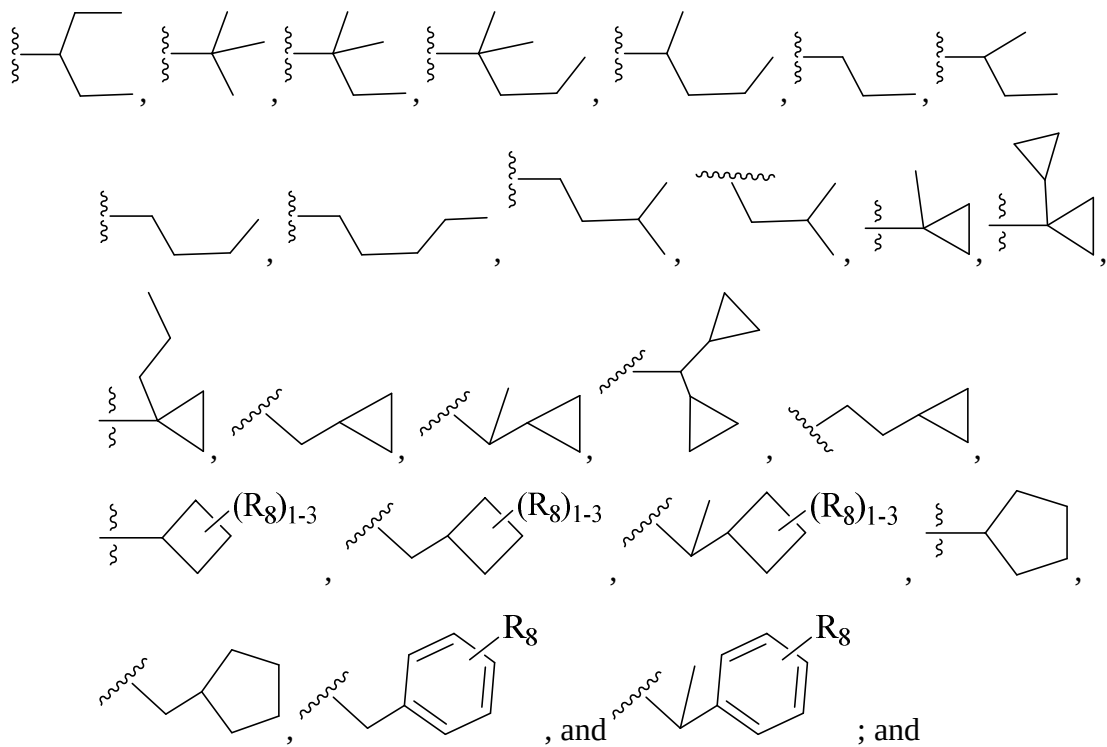
or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

5 R₁₃ is independently selected from H and CH₃;

R₃ is independently selected from H and CH₃;

R_4 is independently selected from



R₅ is independently selected from H, F, and C₁₋₄ alkyl;

R₁₁ is independently selected from -C(=O)OH, and -C(=O)NHSO₂Me.

5



R₂ is independently selected from CH₃ and CD₃;

10

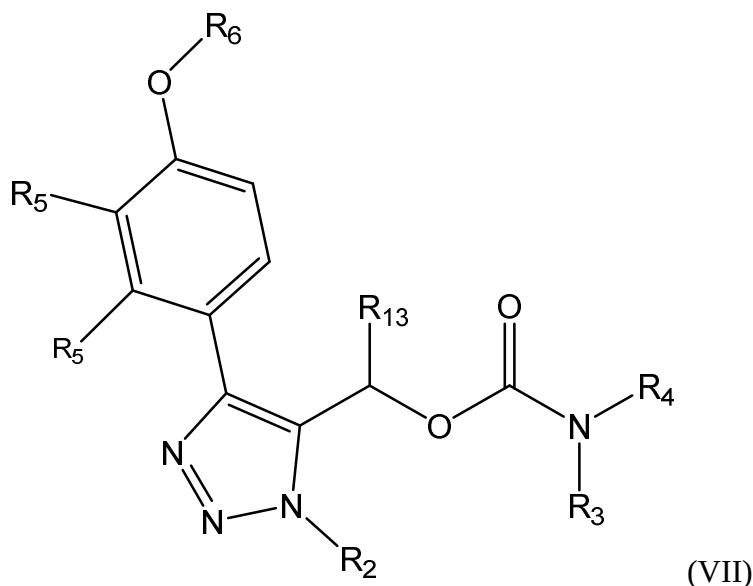
R_4 is independently selected from



R₅ is independently selected from H and CH₃; and

R₈ is independently selected from H, F, Cl, Br, CN, and C₁₋₄ alkyl.

10. The compound of claim 4 having Formula (VII):



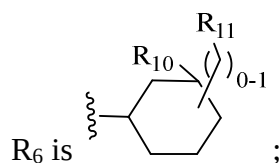
5 or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

R₁₃ is independently selected from H and C₁₋₄ alkyl;

R₃ is independently selected from H and C₁₋₄ alkyl;

10 R₄ is independently selected from C₁₋₆ alkyl substituted with 1-3 R₉, (CR₇R₇)_r-C₃₋₆ cycloalkyl substituted with 1-3 R₈, and -(CR₇R₇)_r-aryl substituted with 1-3 R₈;
R₅ is independently selected from H, F, Cl, CN, and C₁₋₄ alkyl;



15 R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and COOH;

20 R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R_{10} is independently selected from H, C_{1-4} alkyl, and F;
 R_{11} independently selected from $-C(=O)R_{12}$ and tetrazolyl;
 R_{12} is independently selected from OH and $NHSO_2C_{1-4}alkyl$; and
 r is independently selected from zero, 1, 2, 3, and 4.

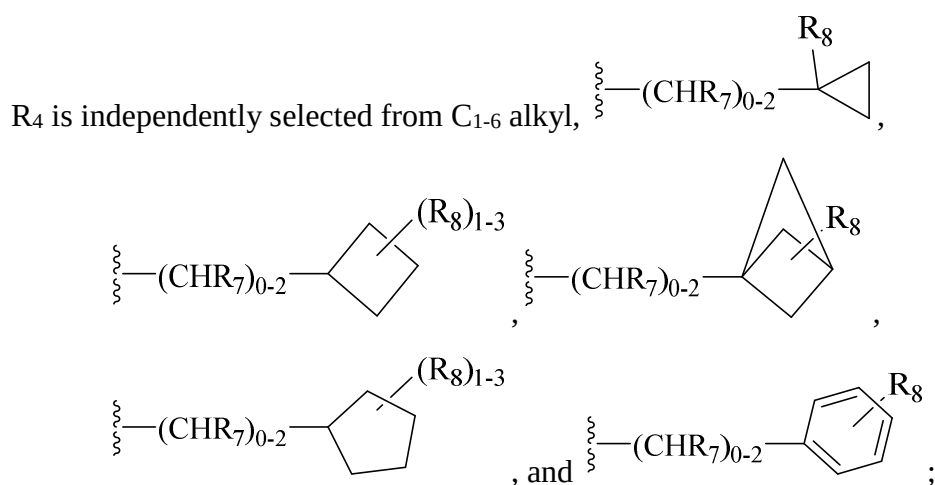
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11. The compound of claim 10, or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

R_2 is independently selected from CH_3 and CD_3 ;

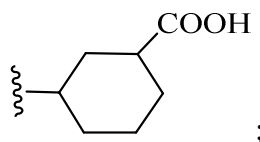
R_{13} is independently selected from H and CH_3 ;

10 R_3 is independently selected from H and CH_3 ;



R_5 is independently selected from H, F, Cl, and C_{1-4} alkyl;

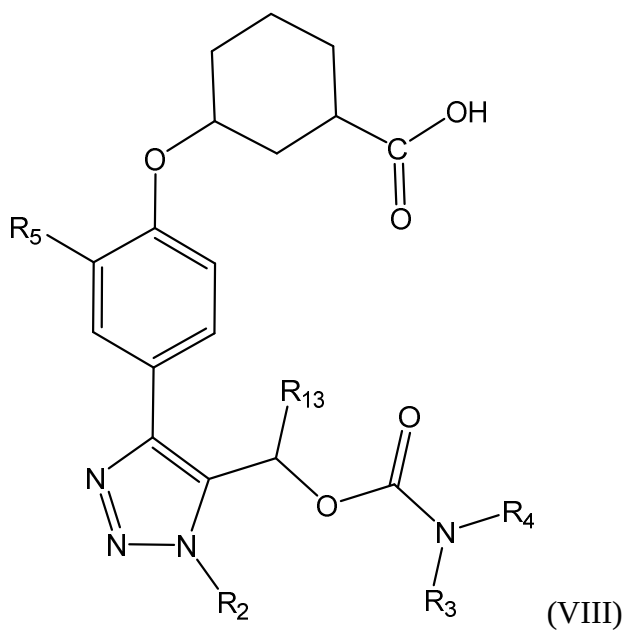
15 R_6 is



R_7 is independently selected from H, C_{1-4} alkyl, and C_{1-6} cycloalkyl; and

R_8 is independently selected from H, F, Cl, Br, CN, and C_{1-4} alkyl.

20 12. The compound of claim 10 having Formula (VIII):



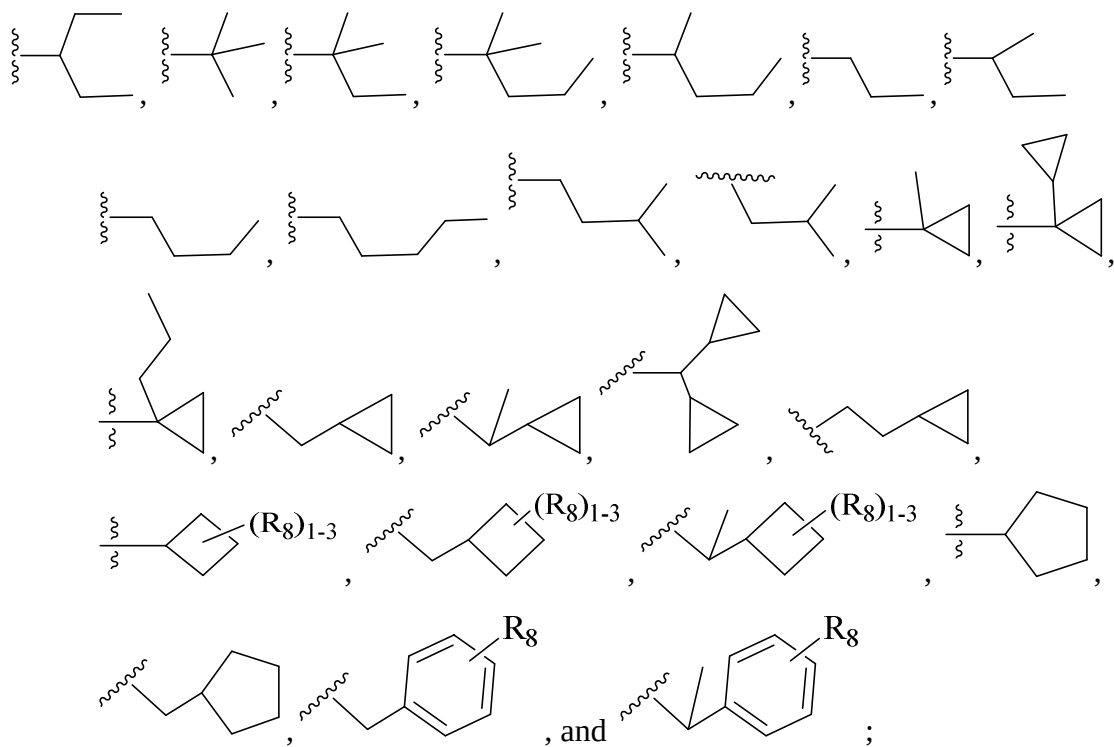
or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

5 R₁₃ is independently selected from H and CH₃;

R₃ is independently selected from H and CH₃;

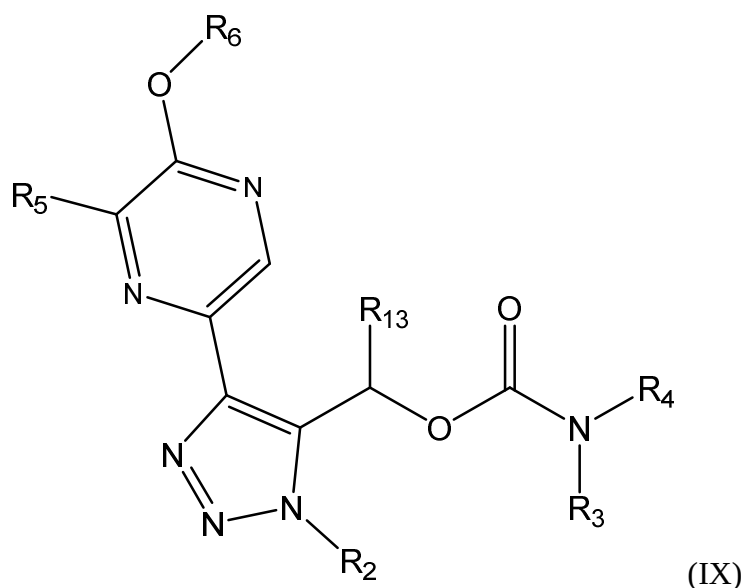
R_4 is independently selected from



R₅ is independently selected from H, F, and CH₃; and

R₈ is independently selected from H, F, Cl, Br, CN, and C₁₋₄ alkyl.

13. The compound of claim 4 having Formula (IX):



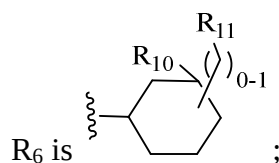
5 or an enantiomer, a diastereomer, a stereoisomer, a pharmaceutically acceptable salt thereof, wherein

R₂ is independently selected from CH₃ and CD₃;

R₁₃ is independently selected from H and C₁₋₄ alkyl;

R₃ is independently selected from H and C₁₋₄ alkyl;

10 R₄ is independently selected from C₁₋₆ alkyl substituted with 1-3 R₉, (CR₇R₇)_r-C₃₋₆ cycloalkyl substituted with 1-3 R₈, and -(CR₇R₇)_r-aryl substituted with 1-3 R₈;
R₅ is independently selected from H, F, Cl, CN, and C₁₋₄ alkyl;



15 R₇ is independently selected from H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; or R₇ and R₇, together with the carbon atom to which they both attach, form a C₃₋₆ cycloalkyl ring;

R₈ is independently selected from H, C₁₋₆ alkyl substituted with 1-5 R₉, C₃₋₆ cycloalkyl, F, Cl, Br, CN, =O, and COOH;

20 R₉ is independently selected from H, F, Cl, NH₂, OH, OC₁₋₅alkyl, C₁₋₅alkyl, C₃₋₆ cycloalkyl, and phenyl, wherein when R₉ is Cl, NH₂ or OH it is not substituted on C₁ of the the alkyl to which it is attached;

R₁₀ is independently selected from H and F;

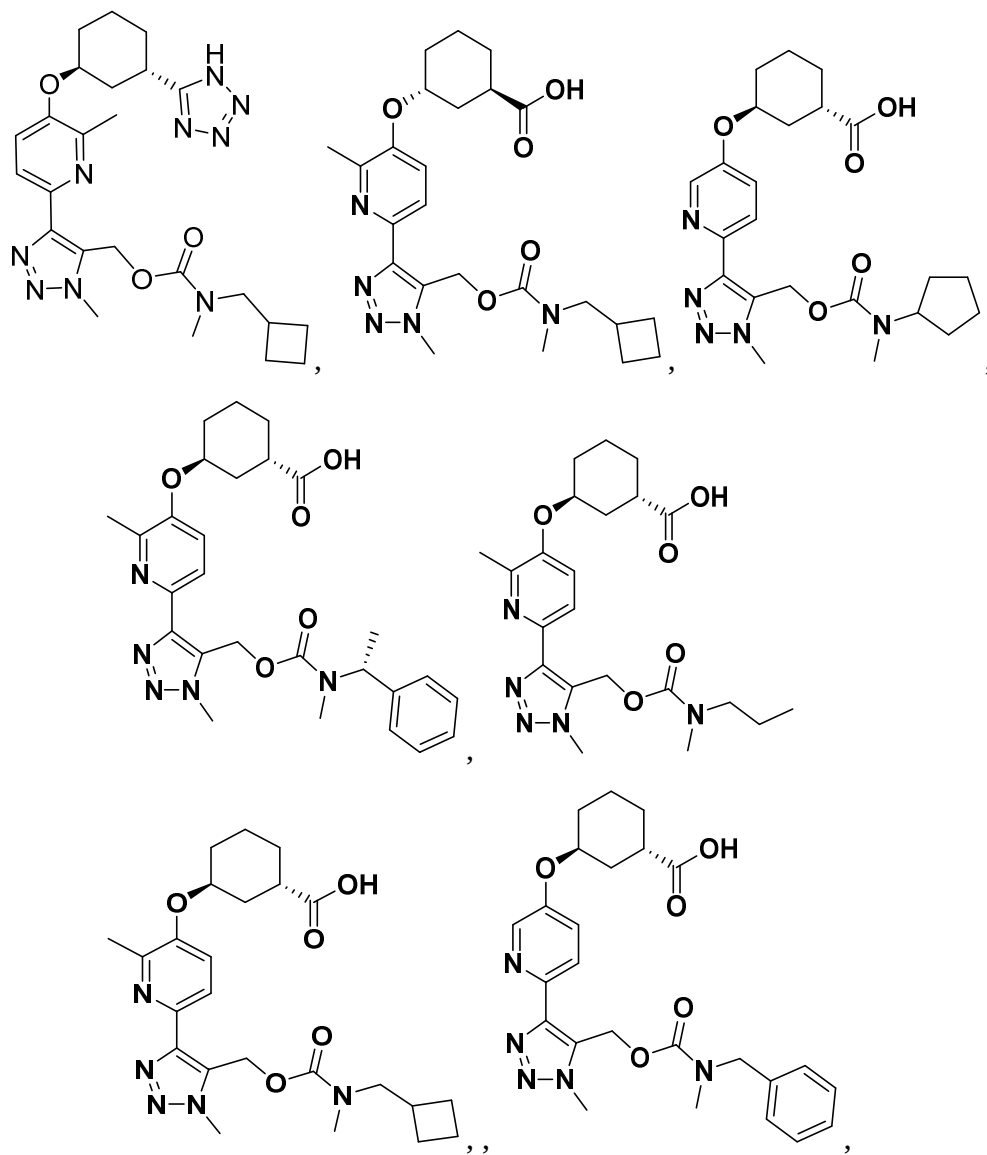
R₁₁ is independently selected from -C(=O)R₁₂ and tetrazolyl;

R₁₂ is independently selected from OH and -C(=O)NHSO₂Me; and

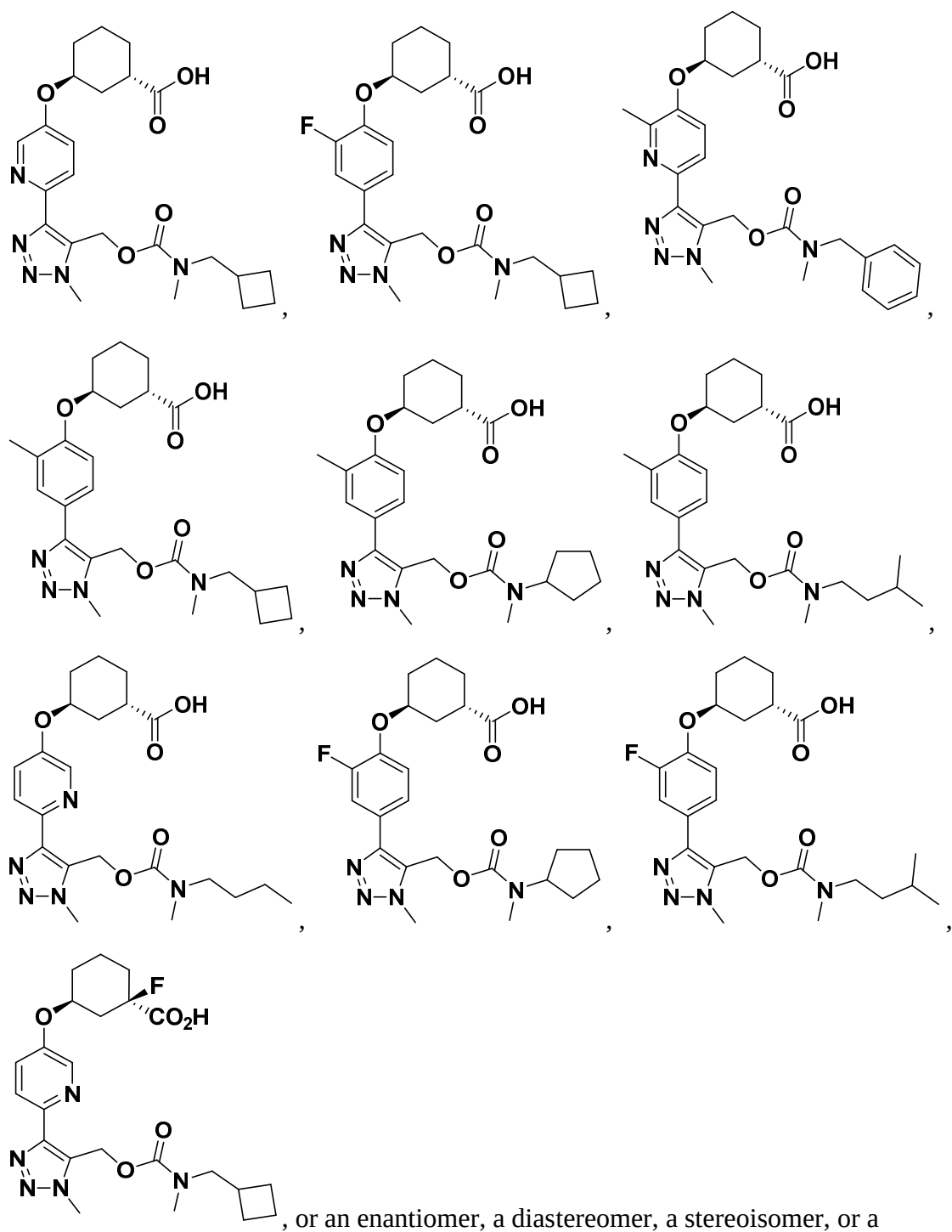
r is independently selected from zero, 1, 2, 3, and 4.

5

14. The compound of claim 4, wherein said compound is selected from the group of:

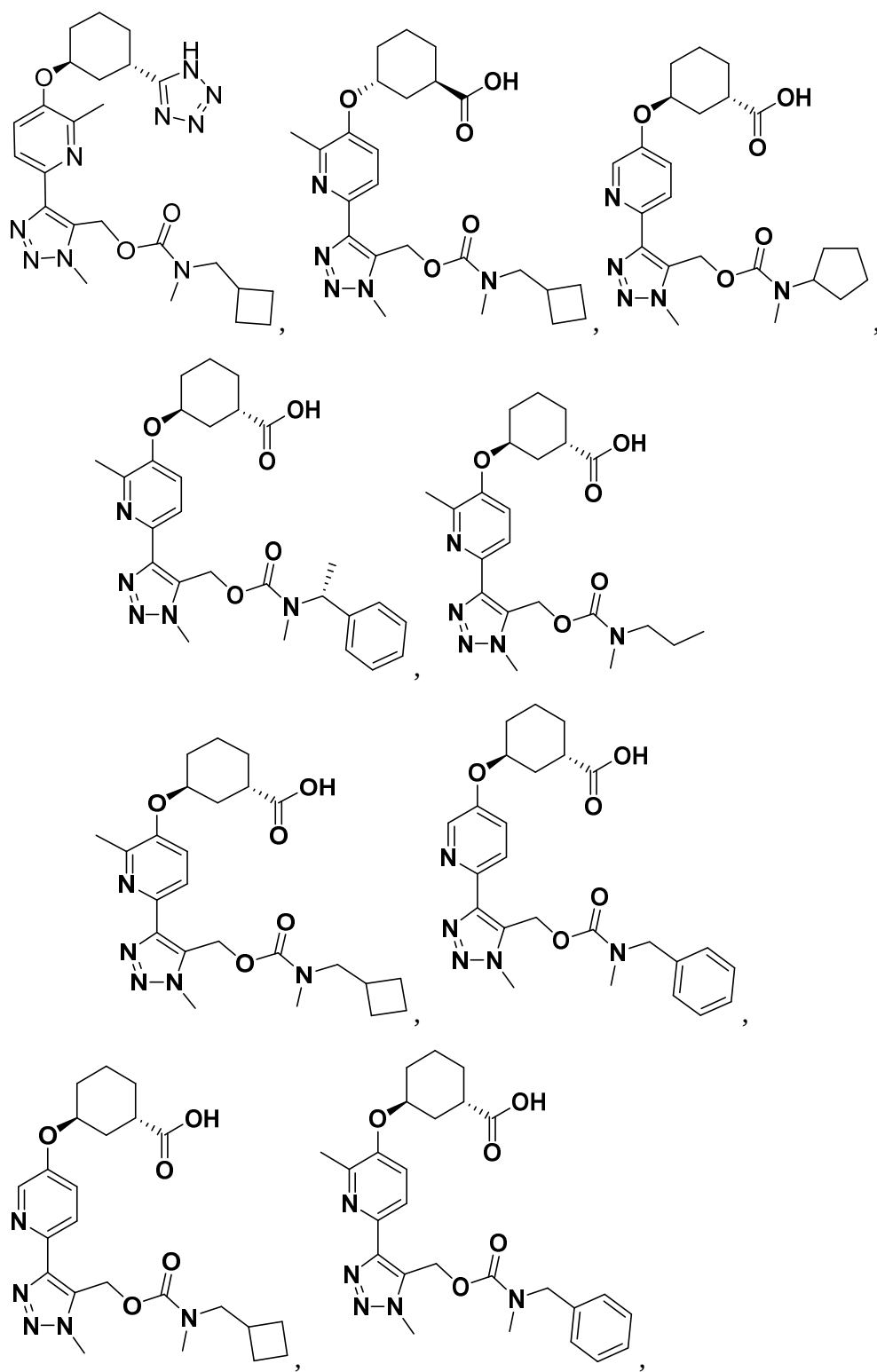


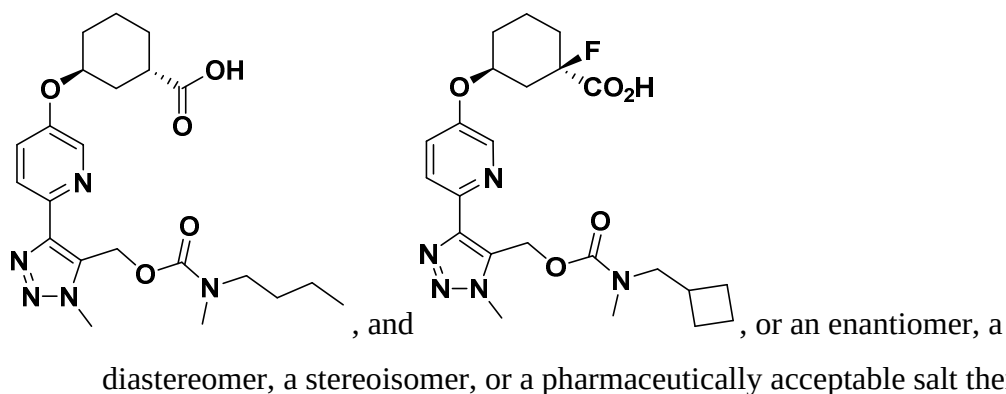
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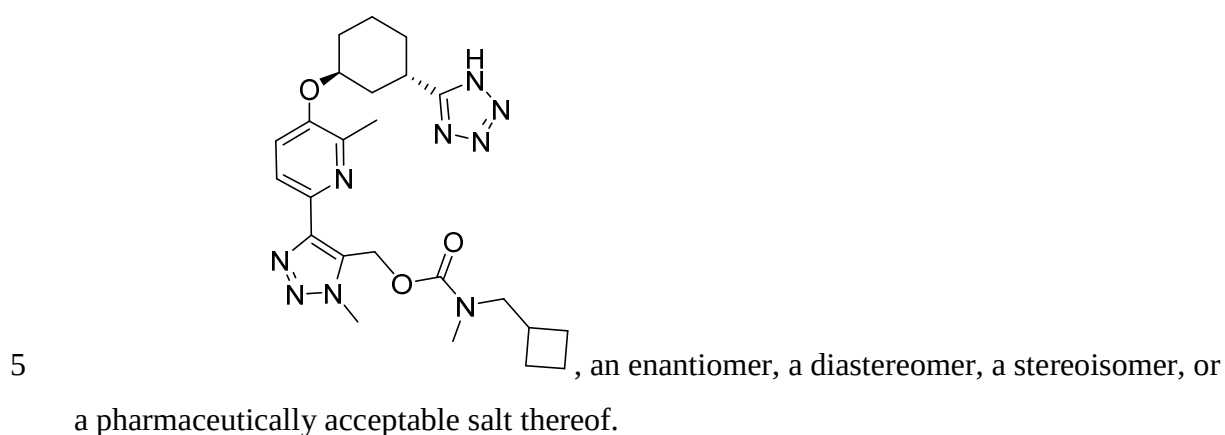
5 pharmaceutically acceptable salt thereof.

15. The compound of claim 4, wherein said compound is selected from the group of:

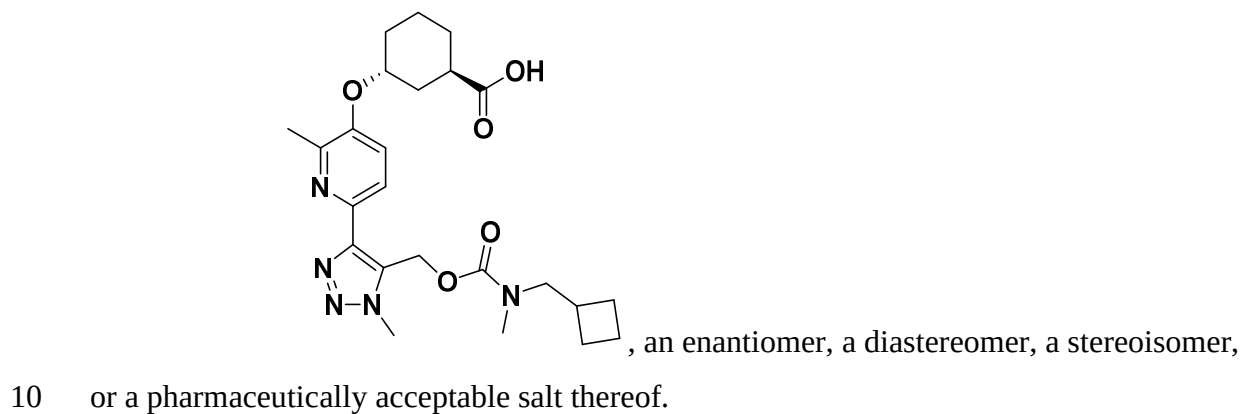




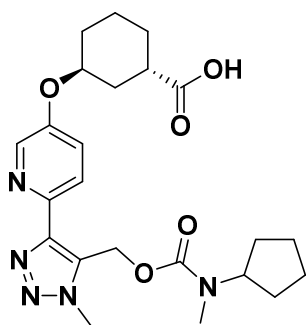
16. The compound of anyone of claims 1-8, wherein said compound has the formula:



17. The compound of anyone of claims 1-8, wherein said compound has the formula:

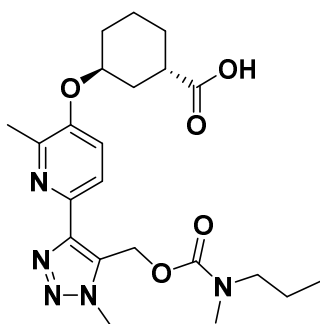


18. The compound of anyone of claims 1-8, wherein said compound has the formula:



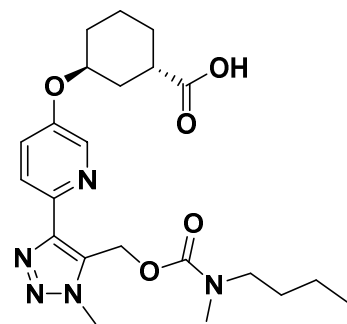
, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

19. The compound of anyone of claims 1-8, wherein said compound has the formula:



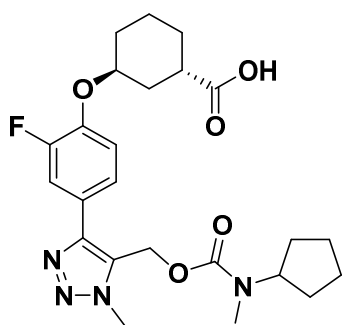
5 , an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

20. The compound of anyone of claims 1-8, wherein said compound has the formula:



10 , an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

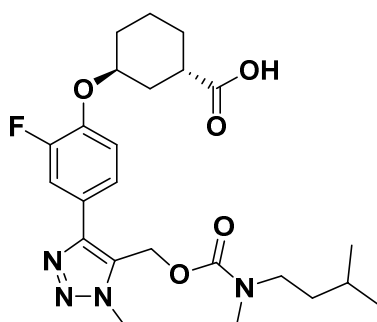
21. The compound of anyone of claims 1-8, wherein said compound has the formula:



, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

22. The compound of anyone of claims 1-8, wherein said compound has the formula:

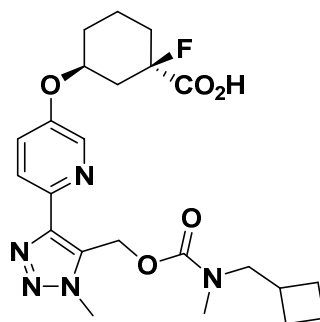
5



, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

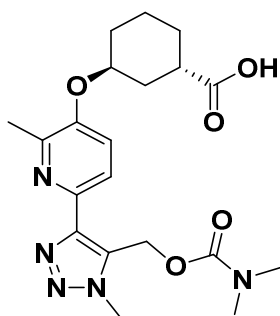
23. The compound of anyone of claims 1-8, wherein said compound has the formula:

10



, or an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

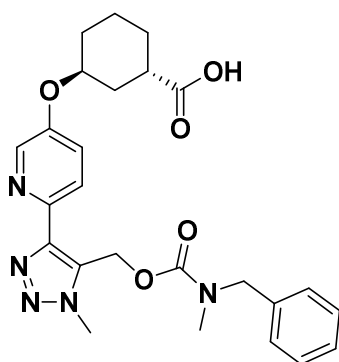
24. The compound of anyone of claims 1-8, wherein said compound has the formula:



, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

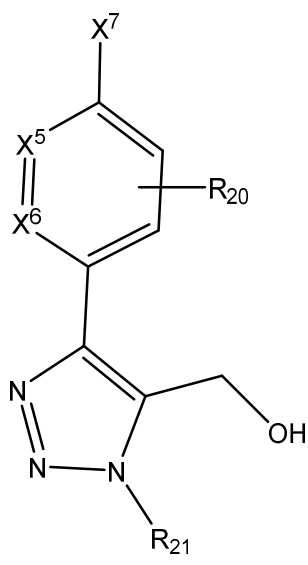
25. The compound of anyone of claims 1-8, wherein said compound has the formula:

5



, an enantiomer, a diastereomer, a stereoisomer, or a pharmaceutically acceptable salt thereof.

26. A compound of Formula (X):

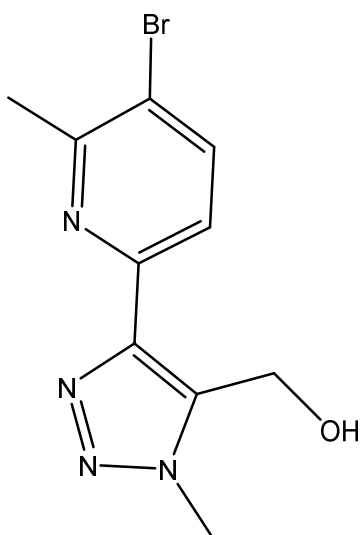


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or an enantiomer, a diastereomer, or a stereoisomer thereof, wherein R_{20} is independently C_{1-6} alkyl or H;

R₂₁ is independently C₁₋₆ alkyl or H;
X⁵ and X⁶ are independently CH or N; and
X⁷ is Br.

- 5 27. The compound of claim 26 having Formula (XI):



(XI), or an enantiomer, a

diastereomer, or a stereoisomer thereof.

10

28. A pharmaceutical composition comprising one or more compounds according to anyone of claims 1-25 and a pharmaceutically acceptable carrier or diluent.

29. A compound according to any one of claims 1-25 for use in therapy.

15

30. A compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof for use in treating fibrosis in a mammal in need thereof.

31. A compound according to any one of claims 1-25 or a pharmaceutically acceptable salt thereof for use in treating lung fibrosis (idiopathic pulmonary fibrosis),
20 asthma, chronic obstructive pulmonary disease (COPD), renal fibrosis, acute kidney injury, chronic kidney disease, liver fibrosis (non-alcoholic steatohepatitis), skin fibrosis, fibrosis of the gut, breast cancer, pancreatic cancer, ovarian cancer, prostate cancer, glioblastoma, bone cancer, colon cancer, bowel cancer, head and neck cancer, melanoma,

multiple myeloma, chronic lymphocytic leukemia, cancer pain, tumor metastasis, transplant organ rejection, scleroderma, ocular fibrosis, age related macular degeneration (AMD), diabetic retinopathy, collagen vascular disease, atherosclerosis, Raynaud's phenomenon, or neuropathic pain in a mammal in need thereof.