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(54) **Title:** LPA RECEPTOR ANTAGONISTS AND USES THEREOF

(57) **Abstract:** The present disclosure relates generally to compounds that bind to Lysophosphatidic Acid Receptor 1 (LPAR1) and act as antagonists of LPAR1. The disclosure further relates to the use of the compounds for the preparation of a medicament for the treatment of diseases and/or conditions through binding of LPAR1, including fibrosis and liver diseases such as non-alcoholic steatohepatitis (NASH), interstitial lung disease (ILD), or chronic kidney disease (CKD).

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LPA RECEPTOR ANTAGONISTS AND USES THEREOF

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/287,252, filed December 8, 2021, which is incorporated herein in its entirety for all purposes.

FIELD

[0002] The present disclosure relates to compounds that bind to and act as antagonists of a lysophosphatidic acid (LPA) receptor, such as LPAR1. The disclosure further relates to the use of the compounds for the treatment and/or prophylaxis of diseases and/or conditions associated with one or more LPA receptors, *e.g.*, an LPAR1 associated disease or condition.

BACKGROUND

[0003] Lysophosphatidic acids (mono-acyl-glycerol-3-phosphate, LPA) are a class of biologically active phospholipids that can be produced from lysophosphatidyl choline (LPC), *e.g.*, by the enzyme autotaxin. A typical LPA has a glycerol, an ester-linked fatty acid at the *sn*-1 position, and a phosphate head group at the *sn*-3 position. LPA with various fatty acids have been identified, including palmitoyl LPA (16:0), stearoyl LPA (18:0), oleoyl LPA (18:1), linoleoyl LPA (18:2) and arachidonyl LPA (20:4). LPA exerts a wide range of cellular responses, such as proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis through a family of rhodopsin-like G protein-coupled receptors (GPCRs). Six LPA receptors have been been characterized and were found to differ in their tissue distribution and downstream signaling pathways. These six LPA receptors are often referred to interchangeably as LPAR1-6 (gene) or LPA1-6 (protein). LPA receptor mediated signaling has been shown to influence many biological processes such as wound healing, immunity, carcinogenesis, angiogenesis and neurogenesis.

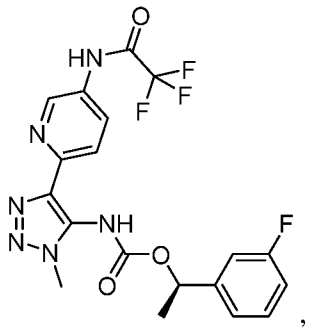
[0004] *In vivo* studies involving LPA receptor-deficient mice or certain tool compounds have suggested a potential of LPA receptors as possible drug targets in a variety of diseases including cancer, fibrosis, inflammation, pain, and cardiovascular diseases. More recently, LPAR1 antagonists have been studied clinically in connection with fibrotic disase states such as idiopathic pulmonary fibrosis (IPF) and systemic sclerosis.

[0005] A need remains for LPA antagonists with desirable selectivity, potency, metabolic stability, or reduced detrimental effects.

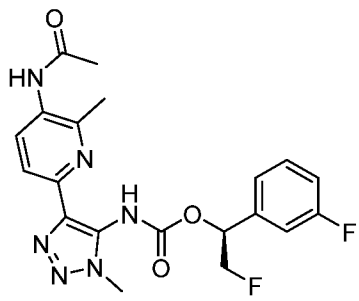
SUMMARY

[0006] The present disclosure provides compounds useful as inhibitors of Lysophosphatidic Acid Receptor 1 (LPAR1). The disclosure further relates to the use of the compounds for the treatment and/or prophylaxis of diseases and/or conditions through binding of LPAR1 by said compounds.

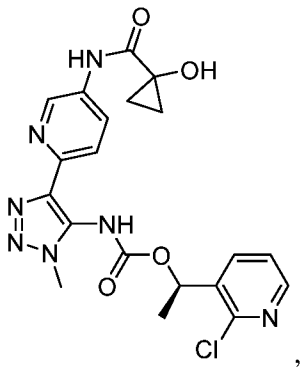
[0007] Provided herein are compounds selected from



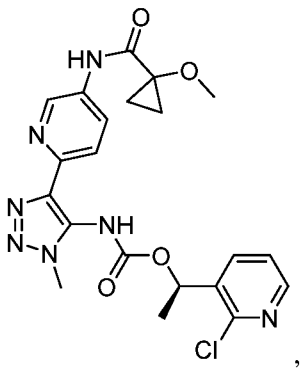
Compound 1



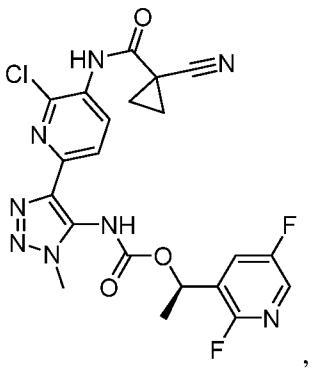
Compound 2



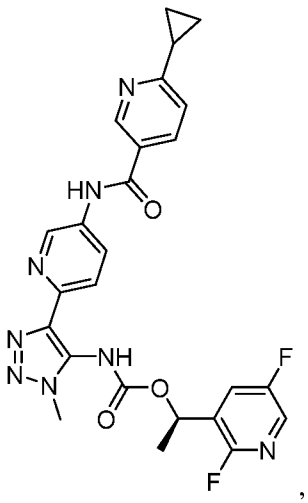
Compound 3



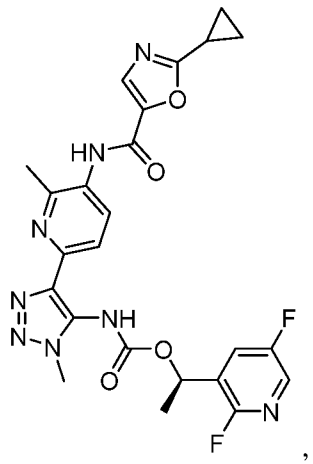
Compound 4



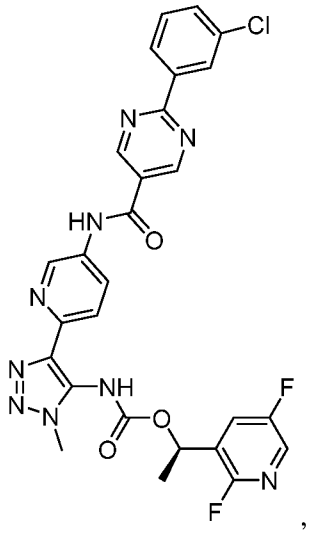
Compound 5



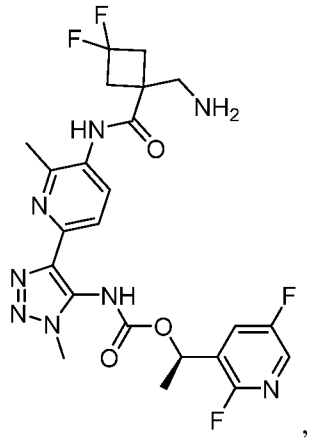
Compound 6



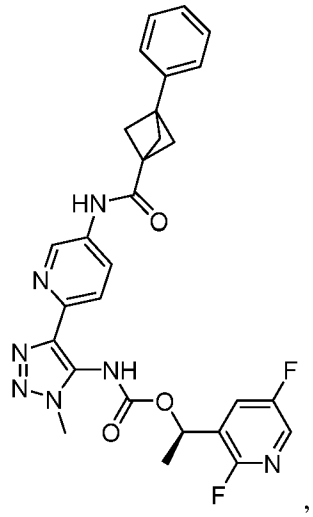
Compound 7



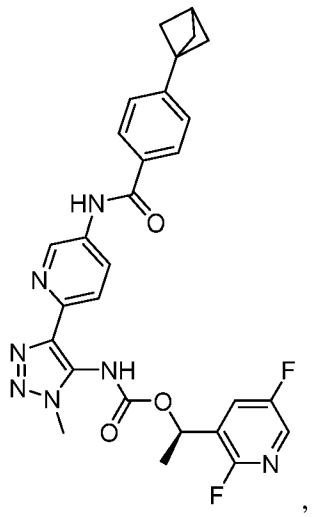
Compound 8



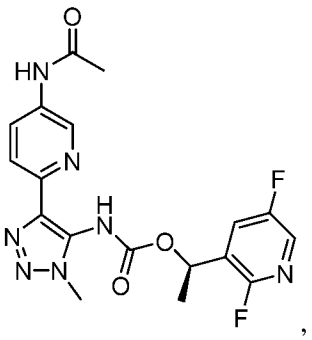
Compound 9



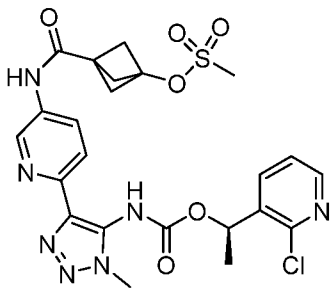
Compound 10



Compound 11



Compound 12

and  , or a pharmaceutically acceptable salt thereof.

Compound 13

[0008] In some embodiments, provided herein are pharmaceutical compositions comprising a compound provided herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier. In some embodiments, the pharmaceutical compositions comprise a therapeutically effective amount of a compound provided herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

[0009] In some embodiments, the pharmaceutical compositions provided herein further comprise one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, or pharmaceutically acceptable salts thereof. In some embodiments, the pharmaceutical compositions further comprise a therapeutically effective amount of the one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, or pharmaceutically acceptable salts thereof.

[0010] In some embodiments, the present disclosure provides methods of inhibiting LPAR1 activity in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Compounds 1-13), or pharmaceutically acceptable salt thereof, or a pharmaceutical composition provided herein.

[0011] In some embodiments, the present disclosure provides methods of treating a patient having an LPAR1 mediated condition, comprising administering to the patient a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Compounds 1-13), or pharmaceutically acceptable salt thereof, or a pharmaceutical composition provided herein.

DETAILED DESCRIPTION

[0012] The present disclosure relates to LPA receptor antagonists, such as antagonists of LPAR1. The disclosure also relates to compositions and methods relating to LPAR1 antagonists and the use of such compounds for treatment and/or prophylaxis of LPAR1-mediated diseases and conditions. The disclosure also relates to compositions and methods of treating and/or preventing liver disease including an LPAR1 antagonist in combination with one or more additional therapeutic agents.

[0013] It is commonly believed that patients with certain LPAR1-mediated diseases, such as cancer, fibrosis, inflammation, pain, and cardiovascular diseases, or liver diseases including non-

alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) can benefit from the treatment with an LPAR1 antagonist and optionally one or more additional therapeutic agents.

Definitions and General Parameters

[0014] The description below is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0015] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, *e.g.*, reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art, and so forth.

[0016] As used in the present specification, the following terms and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0017] "A compound disclosed herein" or "a compound of the present disclosure" or "a compound provided herein" or "a compound described herein" refers to Compounds 1-13.

[0018] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, *e.g.*, reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0019] The disclosures illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising," "including," "containing," etc., shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the disclosure claimed.

[0020] The compounds of the present disclosure can be in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids. The compounds of the present disclosure can be in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids. In case the compounds of the present disclosure contain one or more acidic or basic groups, the disclosure also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the present disclosure which contain acidic groups can be present on these groups and can be used according to the disclosure, for example, as alkali metal salts, alkaline earth metal salts or ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine, amino acids, or other bases known to persons skilled in the art. The compounds of the present disclosure which contain one or more basic groups, *i.e.*, groups which can be protonated, can be present and can be used according to the disclosure in the form of their addition salts with inorganic or organic acids. Examples of suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to persons skilled in the art.

[0021] If the compounds of the present disclosure simultaneously contain acidic and basic groups in the molecule, the disclosure also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to the person skilled in the art like, for example, by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts.

[0022] The present disclosure also includes all salts of the compounds of the present disclosure which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts. Acids and bases useful for reaction with an underlying compound to form pharmaceutically acceptable salts (acid addition or base addition salts respectively) are known to one of skill in the art. Similarly, methods of preparing pharmaceutically acceptable salts from an underlying compound (upon disclosure) are known to one of skill in the art and are disclosed in for example, Berge, at al. Journal of Pharmaceutical Science, Jan. 1977 vol. 66, No.1, and other sources.

[0023] Furthermore, compounds disclosed herein may be subject to tautomerism. Where tautomerism, *e.g.*, keto-enol tautomerism, of compounds or their prodrugs may occur, the individual forms, like, *e.g.*, the keto and enol form, are each within the scope of the disclosure as well as their mixtures in any ratio. The same applies for stereoisomers, like, *e.g.*, enantiomers, cis/trans isomers, diastereomers, conformers, and the like.

[0024] The term "protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. The term "deprotecting" refers to removing the protecting group.

[0025] It will be appreciated by the skilled person that when lists of alternative substituents include members which, because of their valency requirements or other reasons, cannot be used

to substitute a particular group, the list is intended to be read with the knowledge of the skilled person to include only those members of the list which are suitable for substituting the particular group.

[0026] Further the compounds of the present disclosure may be present in the form of solvates, such as those which include as solvate water, or pharmaceutically acceptable solvates, such as alcohols, in particular ethanol. A "solvate" is formed by the interaction of a solvent and a compound.

[0027] In certain embodiments, provided are optical isomers, racemates, or other mixtures thereof of the compounds described herein or a pharmaceutically acceptable salt or a mixture thereof. If desired, isomers can be separated by methods well known in the art, *e.g.*, by liquid chromatography. In those situations, the single enantiomer or diastereomer, *i.e.*, optically active form, can be obtained by asymmetric synthesis or by resolution. Resolution can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using for example, a chiral high-pressure liquid chromatography (HPLC) column.

[0028] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers," which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another. "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0029] Compounds disclosed herein and their pharmaceutically acceptable salts may, in some embodiments, include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. Some embodiments include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate

of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

[0030] Compositions provided herein that include a compound described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof may include racemic mixtures, or mixtures containing an enantiomeric excess of one enantiomer or single diastereomers or diastereomeric mixtures. All such isomeric forms of these compounds are expressly included herein the same as if each and every isomeric form were specifically and individually listed.

[0031] Any structure given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphoros, fluorine and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl and ^{125}I. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0032] The disclosure also includes "deuterated analogs" of compounds disclosed herein, in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds may exhibit increased resistance to metabolism and thus be useful for increasing the half-life of any compound of Formula (I) when administered to a mammal, *e.g.*, a human. *See*, *e.g.*, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are

synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0033] Deuterium labelled or substituted therapeutic compounds of the disclosure may have beneficial DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies.

[0034] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0035] Furthermore, the present disclosure provides pharmaceutical compositions comprising a compound of the present disclosure, or a prodrug compound thereof, or a pharmaceutically acceptable salt or solvate thereof as active ingredient together with a pharmaceutically acceptable carrier.

[0036] "Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present disclosure can encompass any composition made by admixing at least one compound of the present disclosure and a pharmaceutically acceptable carrier.

[0037] As used herein, "pharmaceutically acceptable carrier" includes excipients or agents such as solvents, diluents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like that are not deleterious to the disclosed compound or use

thereof. The use of such carriers and agents to prepare compositions of pharmaceutically active substances is well known in the art (*see*, *e.g.*, Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, PA 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0038] "IC_{50}" or "EC_{50}" refers to the inhibitory concentration required to achieve 50% of the maximum desired effect. In many cases here the maximum desired effect is the inhibition of LPA induced LPAR1 activation. This term is obtained using an *in vitro* assay, such as a calcium mobilization assay, evaluating the concentration-dependent inhibition of LPA induced LPAR1 activity.

[0039] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (*e.g.*, metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (*e.g.*, ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival. In some embodiments, the term "treatment" or "treating" means administering a compound or pharmaceutically acceptable salt of Compounds 1-13 for the purpose of: (i) delaying the onset of a disease, that is, causing the clinical symptoms of the disease not to develop or delaying the development thereof; (ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or (iii) relieving the disease, that is, causing the regression of clinical symptoms or the severity thereof.

[0040] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0041] "Subject" refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

[0042] The term "therapeutically effective amount" or "effective amount" of a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a disease or condition responsive to LPAR1 antagonists. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one or ordinary skill in the art.

List of Abbreviations and Acronyms

Abbreviation	**Meaning**
ACN or MeCN	Acetonitrile
aq.	Aqueous
Bn	Benzyl
COPD	Chronic Obstructive Pulmonary Disease
DCM	Dichloromethane
DIEA	N, N-Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide

EA	Ethyl acetate
EDTA	Ethylenediaminetetraacetic acid
ESI	Electronspray Ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
h or hr(s)	Hour(s)
HBSS	Hanks' Balanced Salt solution
HCC	Hepatocellular carcinoma
HPLC	High performance liquid chromatography
LCMS or LC/MS	Liquid Chromatography Mass Spectrometry
LPA	Lysophosphatidic acid
LPC	Lysophosphatidylcholine
Me	Methyl
MeOH	Methanol
MS	Mass Spectrometry
m/z	Mass-to-charge ratio
NADPH	Dihydronicotinamide-adenine dinucleotide phosphate
NAFLD	Non-alcoholic fattyl liver disease
NASH	Non-alcoholic steatohepatitis
NMR	Nuclear Magnetic Resonance spectroscopy

PBC	Primary Biliary Cirrhosis
PE	Petroleum ether
PSC	Primary Sclerosing Choleangitis
rpm	Revolutions per minute
RT or rt	Room temperature
sat.	Saturated
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
T3P	Propanephosphonic acid anhydride

[0043] As used herein, an "LPAR1 antagonist" refers to any agent that is capable of binding and inhibiting LPAR1. LPAR1, also known as LPA_1, is a GPCR that binds the lipid signaling molecule lysophosphatidic acid (LPA). Exemplary reference sequences for LPAR1 include the NCBI Reference Sequences NP_001392 (human protein), NP_001277415 (mouse protein), NM_001401 (human mRNA), and NM_001290486 (mouse mRNA). LPAR1 antagonists can act as competitive inhibitors of full or partial LPAR1 agonists, or as inverse agonists. The activity of an LPAR antagonist may be measured by methods known in the art, such as those described and cited in Castelino *et al.*, 2010 Arthritis Rheum. 2011 May; 63(5): 1405–1415 or Swaney *et al.*, J Pharmacol Exp Ther. 2011 Mar;336(3):693-700.

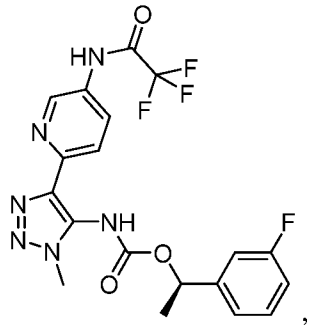
[0044] As used herein, an "ACC inhibitor" refers to any agent that is capable of binding and inhibiting Acetyl-CoA carboxylase (ACC). ACC inhibitors can act as inhibitors or partial inhibitors of ACC. The agent can be a chemical compound or biological molecule (*e.g.*, a protein or antibody). The activity of an ACC inhibitor can be measured by methods known in the art, such as those described and cited in U.S. Patent No. 8,969,557 and/or in U.S. Patent No.10,208,063, both of which are incorporated herein by reference in their entirety.

[0045] As referred to herein, an "ASK1 inhibitor" can be any agent that is capable of inactivating an apoptosis signal regulating kinase 1 (ASK1) protein. The agent can be a chemical compound or biological molecule (*e.g.*, a protein or antibody). The ASK1 protein activity can be measured by several different methods. For example, the activity of an ASK1 protein can be determined based on the ability of the ASK1 protein to phosphorylate a substrate protein. Methods for identifying an ASK1 inbibitor are known (*see*, *e.g.*, U.S. 2007/0276050). Exemplary ASK1 substrate proteins include MAPKK3, MAPKK4, MAPKK6, MAPKK7, or fragments thereof. The ASK1 protein activity can also be measured by the phosphorylation level of the ASK1 protein, for example, the phosphorylation level of a threonine residue in the ASK1 protein corresponding to threonine 838 (T838) of a human full-length ASK1 protein or threonine 845 (T845) of a mouse full-length ASK1 protein. For example, where the ASK1 protein comprises a full-length human ASK1 protein sequence, an ASK1 inhibitor may attenuate phosphorylation of T838 in the full-length human ASK1 protein sequence. A site-specific antibody against human ASK1 T838 or mouse ASK1 T845 may be used to detect the phosphohorylation level.

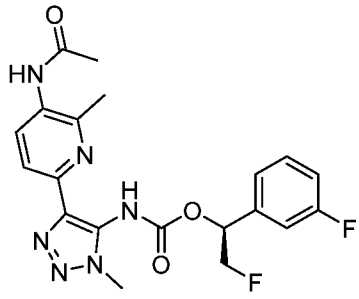
[0046] As used herein, a "FXR agonist" refers to any agent that is capable of binding and activating farnesoid X receptor (FXR) which can be referred to as bile acid receptor (BAR) or NR1H4 (nuclear receptor subfamily 1, group H, member 4) receptor. FXR agonists can act as agonists or partial agonists of FXR. The agent can be a chemical compound or biological molecule (*e.g.*, a protein or antibody). The activity of an FXR agonist can be measured by several different methods, *e.g.*, in an in vitro assay using the fluorescence resonance energy transfer (FRET) cell free assay as described in Pellicciari, et al. Journal of Medicinal Chemistry, 2002 vol. 15, No. 45:3569-72.

Compounds

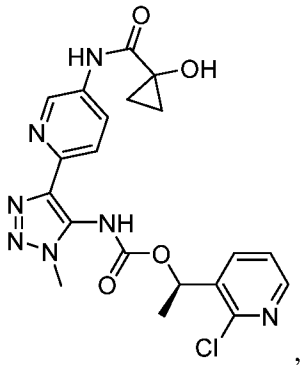
[0047] Provided herein are compounds selected from



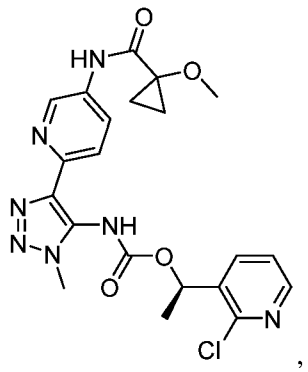
Compound 1



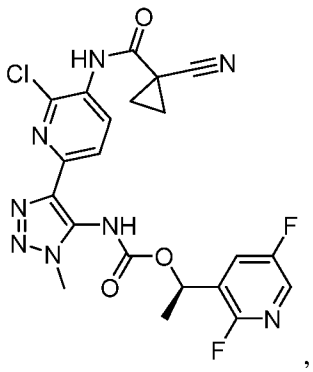
Compound 2



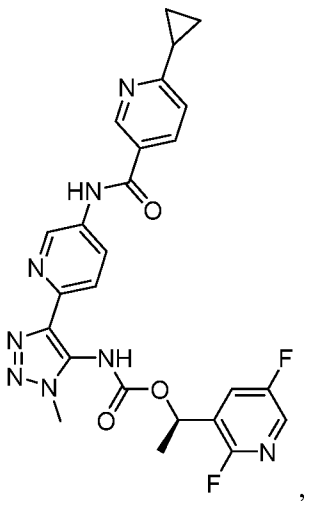
Compound 3



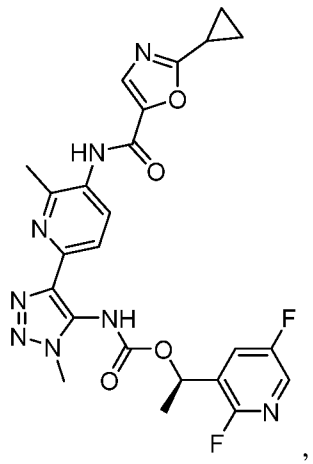
Compound 4



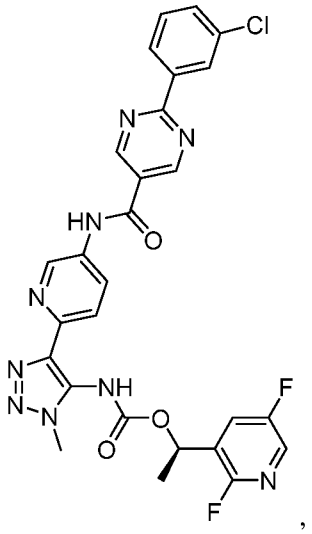
Compound 5



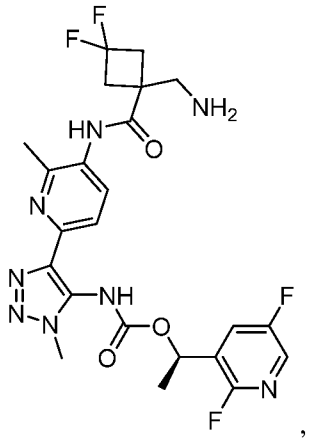
Compound 6



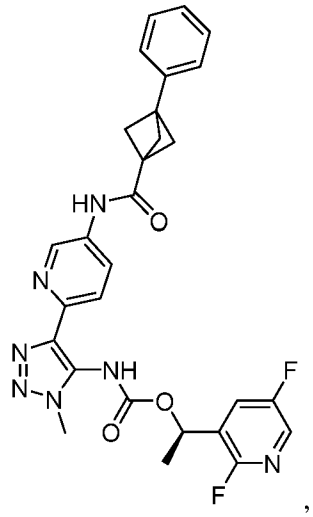
Compound 7



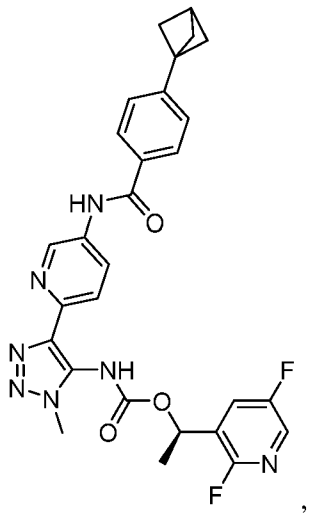
Compound 8



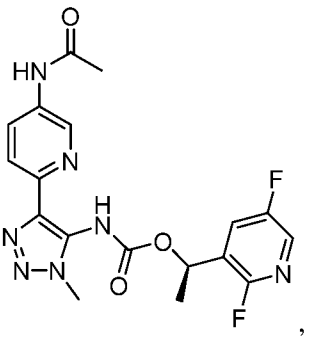
Compound 9



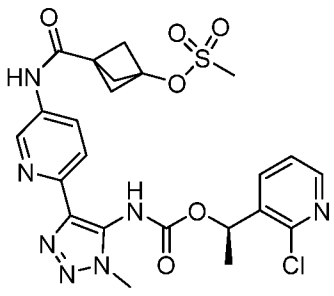
Compound 10



Compound 11

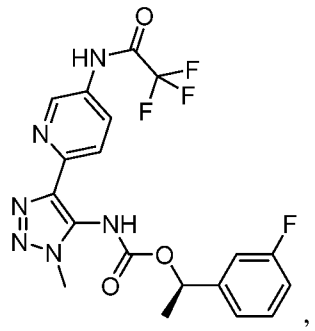


Compound 12

and  , or a pharmaceutically acceptable salt thereof.

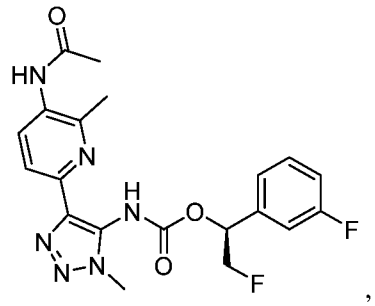
Compound 13

[0048] In some embodiments, the compound is Compound 1 having the structure:



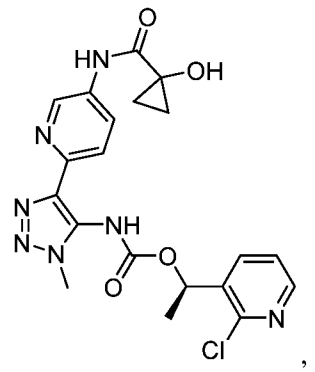
or pharmaceutically acceptable salt thereof.

[0049] In some embodiments, the compound is Compound 2 having the structure:



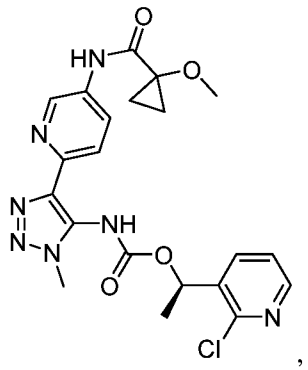
or pharmaceutically acceptable salt thereof.

[0050] In some embodiments, the compound is Compound 3 having the structure:



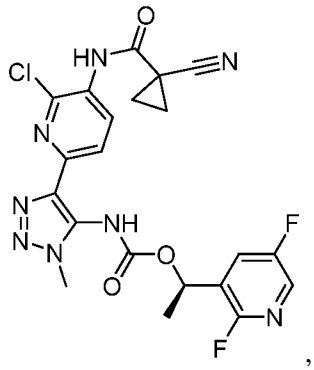
or pharmaceutically acceptable salt thereof.

[0051] In some embodiments, the compound is Compound 4 having the structure:



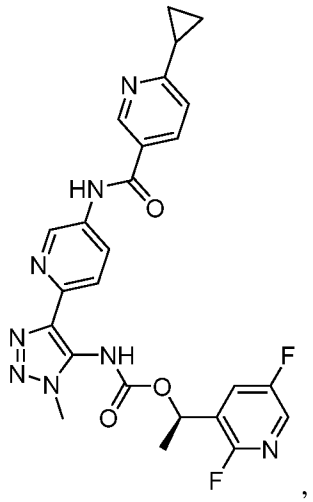
or pharmaceutically acceptable salt thereof.

[0052] In some embodiments, the compound is Compound 5 having the structure:



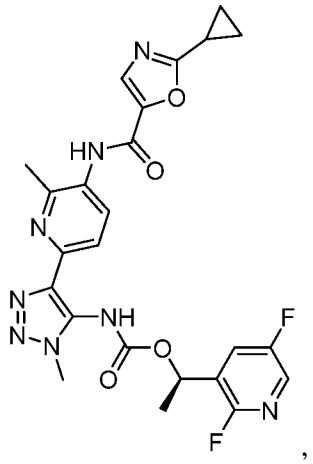
or pharmaceutically acceptable salt thereof.

[0053] In some embodiments, the compound is Compound 6 having the structure:



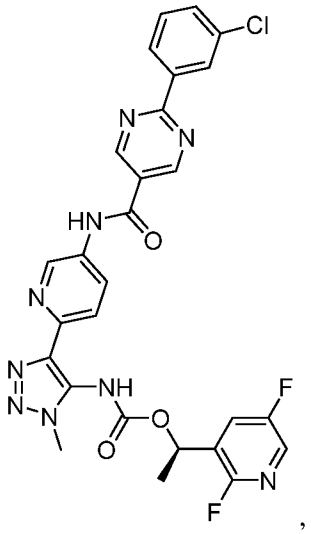
or pharmaceutically acceptable salt thereof.

[0054] In some embodiments, the compound is Compound 7 having the structure:



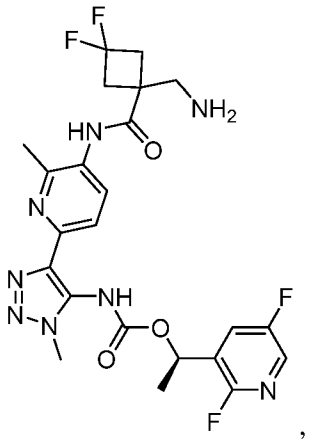
or pharmaceutically acceptable salt thereof.

[0055] In some embodiments, the compound is Compound 8 having the structure:



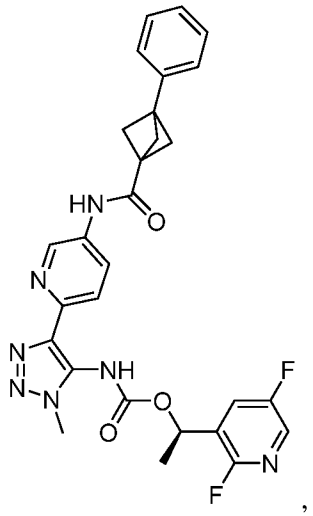
or pharmaceutically acceptable salt thereof.

[0056] In some embodiments, the compound is Compound 9 having the structure:



or pharmaceutically acceptable salt thereof.

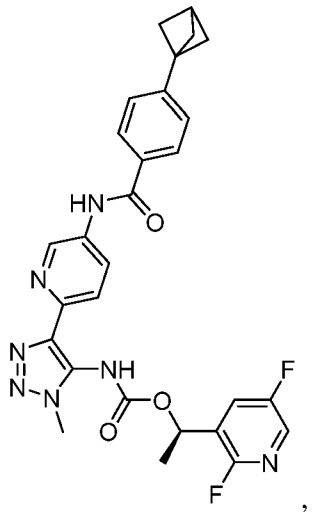
[0057] In some embodiments, the compound is Compound 10 having the structure:



,

or pharmaceutically acceptable salt thereof.

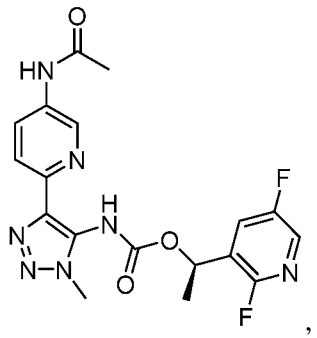
[0058] In some embodiments, the compound is Compound 11 having the structure:



,

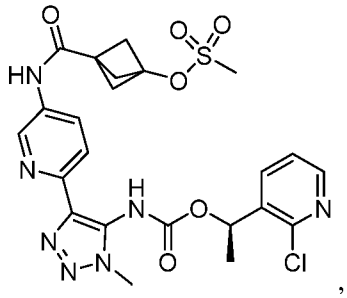
or pharmaceutically acceptable salt thereof.

[0059] In some embodiments, the compound is Compound 12 having the structure:



or pharmaceutically acceptable salt thereof.

[0060] In some embodiments, the compound is Compound 13 having the structure:



or pharmaceutically acceptable salt thereof.

Pharmaceutical Compositions and Modes of Administration

[0061] Furthermore, the present disclosure provides pharmaceutical compositions comprising at least one compound of the present disclosure, or a prodrug compound thereof, or a pharmaceutically acceptable salt or solvate thereof as active ingredient together with a pharmaceutically acceptable carrier.

[0062] The pharmaceutical composition of the present disclosure may additionally comprise one or more other compounds as active ingredients like a prodrug compound or other enzyme inhibitors.

[0063] The compositions are suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation) or nasal administration, although the most suitable route in any given case will depend

on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

[0064] In practical use, the compounds of the present disclosure can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

[0065] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or non-aqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

[0066] The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

[0067] Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir

may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

[0068] In some embodiments, the compounds of the present disclosure may also be used as salts with various countercations to yield an orally available formulation.

[0069] The compounds of the present disclosure may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0070] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[0071] Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present disclosure. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. In some embodiments, compounds of the present disclosure are administered orally.

Kits

[0072] Provided herein are also kits that include a compound of the disclosure, or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof, and suitable packaging. In one embodiment, a kit further includes instructions for use. In one aspect, a kit includes a compound of the disclosure, or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or

deuterated analog thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[0073] Provided herein are also articles of manufacture that include a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe, and intravenous bag.

Treatment Methods and Uses

[0074] The disclosure further relates to the use of compounds disclosed herein for the treatment and/or prophylaxis of diseases and/or conditions through binding of LPAR1 by said compounds. Further, the present disclosure relates to the use of said compounds for the preparation of a medicament for the treatment and/or prophylaxis of diseases and/or conditions through binding of LPAR1 by said compounds.

[0075] Medicaments as referred to herein may be prepared by conventional processes, including the combination of a compound according to the present disclosure and a pharmaceutically acceptable carrier.

[0076] In some embodiments, provided herein is a method of treating and/or preventing an LPAR1-mediated disease or condition in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Compounds 1-13, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Compounds 1-13, or a pharmaceutically acceptable salt thereof.

[0077] In some embodiments, the LPAR1-mediated disease or condition includes those wherein an absolute or relative excess of LPA is present and/or observed.

[0078] In some embodiments, the LPAR1-mediated disease or condition includes fibrosis, wound healing, cancer, pain, respiratory disorders, allergic disorders, nervous system disorders, cardiovascular disorders, or inflammatory disorders.

[0079] In some embodiments, the LPAR1-mediated disease or condition is an interstitial lung disease (ILD). In some embodiments, the interstitial lung disease (ILD) is nonspecific interstitial pneumonitis (NSIP), sarcoidosis, asbestosis, an ILD related to an occupational exposure,

progressive fibrosing ILD, idiopathic interstitial pneumonia (IIP), connective tissue disease-associated interstitial lung disease (CTD-ILD), rheumatoid arthritis-associated ILD, scleroderma-associated ILD, or extrinsic alveolar alveolitis.

[0080] In some embodiments, the LPAR1-mediated disease or condition is a chronic kidney disease (CKD). In some embodiments, the chronic kidney disease is complement glomerulopathy, membranous glomerulopathy, polycystic kidney disease, IgA nephropathy, focal segmental glomerulosclerosis (FSGS), or Alport Syndrome.

[0081] In some embodiments, the LPAR1-mediated disease or condition includes fibrosis. In some embodiments, fibrosis includes pulmonary fibrosis, renal fibrosis, hepatic fibrosis, ocular fibrosis, or cardiac fibrosis.

[0082] In some embodiments, the LPAR1-mediated disease or condition includes pulmonary fibrosis. In some embodiments, pulmonary fibrosis includes idiopathic pulmonary fibrosis (IPF). In some embodiments pulmonary fibrosis includes Progressive Fibrotic interstitial lung disease (PF-ILD). In some embodiments, pulmonary fibrosis includes 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).

[0083] In some embodiments, the LPAR1-mediated disease or condition includes renal fibrosis. In some embodiments, renal fibrosis includes chronic nephropathies associated with injury/ibrosis (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.

[0084] In some embodiments, the LPAR1-mediated disease or condition includes liver fibrosis. In some embodiments, liver fibrosis includes liver 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.

[0085] In some embodiments, the LPAR1-mediated disease or condition includes head and neck fibrosis, *e.g.*, radiation induced.

[0086] In some embodiments, the LPAR1-mediated disease or condition includes corneal scarring, *e.g.*, due to LASIK (laser-assisted in situ keratomileusis), corneal transplantation, or trabeculectomy. In some embodiments, a compound of Compounds 1-13, or a pharmaceutically acceptable salt thereof, is used to improve the corneal sensitivity decrease caused by corneal operations such as LASIK or cataract operation, corneal sensitivity decrease caused by corneal degeneration, and dry eye symptom caused thereby. In some embodiments, a compound of Compounds 1-13, or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of ocular inflammation and allergic conjunctivitis, vernal keratoconjunctivitis, and papillary conjunctivitis. In some embodiments, a compound of Compounds 1-13, or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of Sjogren disease or inflammatory disease with dry eyes.

[0087] In some embodiments, the LPAR1-mediated disease or condition includes another fibrotic condition, such as hypertrophic scarring and keloids, *e.g.*, burn induced or surgical, sarcoidosis, scleroderma, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, mixed connective tissue disease, and Peyronie's disease.

[0088] In some embodiments, the LPAR1-mediated disease or condition includes pain. In some embodiments, pain includes neuropathic pain. In some embodiments, pain includes acute pain. In some embodiments, pain includes chronic pain.

[0089] In some embodiments, the LPAR1-mediated disease or condition includes cancer. In some embodiments, cancer includes ovarian cancer, colon cancer, prostate cancer, breast cancer, melanoma, head and neck cancer, bowel cancer (colorectal cancer), and thyroid cancer. In some embodiments, cancer includes solid tumors, such as (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias) at any stage of the disease with or without metastases. In some embodiments, cancer includes, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid

tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hair) cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenstrom macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primiti ve neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastema, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sezary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive, neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.

[0090] In some embodiments, the LPAR1-mediated disease or condition includes a respiratory or allergic disorder. In some embodiments, the respiratory or allergic disorder includes asthma,

peribronchiolar fibrosis, obliterative bronchiolitis, and chronic obstructive pulmonary disease (COPD). In some embodiments, the COPD includes chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation, and cystic fibrosis. In some embodiments, the respiratory disease includes 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-mduced 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, and hypoxia.

[0091] In some embodiments, the LPAR1-mediated disease or condition includes a nervous system disorder. In some embodiments, the nervous system disorder includes Alzheimer's Disease, cerebral edema, cerebral ischemia, stroke, multiple sclerosis, neuropathies, Parkinson's Disease, a nervous condition found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or bram stem injury), as well as the neurological aspects of disorders such as degenerative disk disease and sciatica.

[0092] In some embodiments, the LPAR1-mediated disease or condition includes a cardiovascular disorder. In some embodiments, the cardiovascular disorder includes arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis; stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension; valvular heart disease; heart failure; abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, and a cardiovascular insufficiency limited to a single organ or tissue.

[0093] In some embodiments, the LPAR1-mediated disease or condition includes lung fibrosis, kidney fibrosis, liver fibrosis, scarring, asthma, rhinitis, chronic obstructive pulmonary disease (COPD), 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.

[0094] In some embodiments, the LPAR1-mediated disease or condition is a liver disease. In some embodiments, the liver disease is hepatitis C, liver cancer, familial combined hyperlipidemia, non-alcoholic fatty liver disease (NAFLD), progressive familial intrahepatic cholestasis, primary biliary cirrhosis (PBC), or (PSC). In some embodiments, the liver disease is PSC. In some embodiments the liver disease comprises portal hypertension. In some embodiments, liver cancer comprises hepatocellular carcinoma (HCC), cholangiocarcinoma, angiosarcoma, or hemangiosarcoma. In some embodiments, liver cancer comprises HCC. In some embodiments, NAFLD comprises steatosis. In some embodiments, NAFLD comprises NASH. In some embodiments, NAFLD or NASH comprises liver fibrosis. In some embodiments, NAFLD or NASH comprises liver cirrhosis. In some embodiments, the NAFLD or NASH comprises compensated liver cirrhosis. In some embodiments, the NAFLD or NASH comprises decompensated liver fibrosis. In some embodiments, the NAFLD comprises HCC. In some embodiments, the liver disease is NASH.

[0095] In some embodiments, provided herein is a method of treating and/or preventing NAFLD or NASH in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Compounds 1-13, or pharmaceutically acceptable salt thereof, or a composition comprising a compound of Compounds 1-13, or pharmaceutically acceptable salt thereof. In some embodiments, NAFLD or NASH comprise liver fibrosis. In some embodiments, NAFLD or NASH comprise liver cirrhosis. In some embodiments, liver cirrhosis is compensated liver cirrhosis. In some embodiments, liver cirrhosis is decompensated liver cirrhosis. In some embodiments NAFLD or NASH comprise HCC.

[0096] In some embodiments, provided herein is a method of preventing a liver disease or condition in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Compounds 1-13, or pharmaceutically acceptable salt thereof, or a composition comprising a compound of Compounds 1-13, or pharmaceutically acceptable salt thereof. In some embodiments, the liver disease or condition is liver fibrosis. In some embodiments, the liver disease or condition is liver cirrhosis. In some embodiments, liver cirrhosis is compensated liver cirrhosis. In some embodiments, liver cirrhosis is decompensated liver cirrhosis. In some embodiments, the liver disease or condition is HCC.

[0097] In some embodiments, the present disclosure relates to the use of Compounds 1-13, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for the prophylaxis and/or treatment of an LPAR1-mediated disease or condition disclosed herein.

Dosage

[0098] The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

[0099] When treating or preventing an LPAR1 mediated disease or condition for which compounds of the present disclosure are indicated, generally satisfactory results are obtained when the compounds of the present disclosure are administered at a daily dosage of from about 0.1 milligram to about 300 milligram per kilogram of animal body weight. In some embodiments, the compounds of the present disclosure are given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1 milligram to about 1000 milligrams, or from about 1 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.1 milligrams to about 200 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response. In some embodiments, the total daily dosage is from about 1 milligram to about 900 milligrams, about 1 milligram to about 800 milligrams, about 1 milligram to about 700 milligrams, about 1 milligram to about 600 milligrams, about 1 milligram to about 400 milligrams, about 1 milligram to about 300 milligrams, about 1 milligram to about 200 milligrams, about 1 milligram to about 100 milligrams, about 1 milligram to about 50 milligrams, about 1 milligram to about 20 milligram, or about 1 milligram to about 10 milligrams.

[0100] The compounds of the present application or the compositions thereof may be administered once, twice, three, or four times daily, using any suitable mode described above. Also, administration or treatment with the compounds may be continued for a number of days; for example, commonly treatment would continue for at least 7 days, 14 days, or 28 days, for one cycle of treatment. Treatment cycles are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in other embodiments, may also be continuous.

[0101] In some embodiments, the methods provided herein comprise administering to the subject an initial daily dose of about 1 to 800 mg of a compound described herein and increasing the dose by increments until clinical efficacy is achieved. Increments of about 5, 10, 25, 50, or 100 mg can be used to increase the dose. The dosage can be increased daily, every other day, twice per week, or once per week.

Combinations

[0102] In some embodiments, a compound of Compounds 1-13 provided herein, or pharmaceutically acceptable salt thereof, is administered in combination with one or more additional therapeutic agents to treat or prevent a disease or condition disclosed herein. In some embodiments, the one or more additional therapeutic agents are one, two, three, or four additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are one additional therapeutic agent. In some embodiments, the one or more additional therapeutic agents are two additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are three additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are four additional therapeutic agents.

[0103] In some embodiments, the pharmaceutical compositions provided herein have a compound of Compounds 1-13 provided herein, or pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are one, two, three, or four additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are one additional therapeutic agent. In some embodiments, the one or more additional therapeutic agents are two additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are three additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are four additional therapeutic agents.

[0104] In some embodiments, the one or more additional therapeutic agents are selected from a(n) angiotensin converting enzyme (ACE) inhibitor, Adenosine A3 receptor agonist, Adiponectin receptor agonist, AKT protein kinase inhibitor, AMP kinase activator, AMP-activated protein kinase (AMPK) activator, Amylin receptor agonist, Angiotensin II AT-1 receptor antagonist, Androgen receptor agonist, Apoptosis signal-regulating kinase 1 (ASK1) inhibitor, ATP citrate lyase inhibitor, Apolipoprotein C3 (APOC3) antagonist, Autophagy protein modulator, Autotaxin

inhibitors, Axl tyrosine kinase receptor inhibitor, Bax protein stimulator, Bioactive lipid, Calcitonin agonist, Cannabinoid receptor modulator, Caspase inhibitor, Caspase-3 stimulator, Cathepsin inhibitor (*e.g.*, cathepsin B inhibitor), Caveolin 1 inhibitor, CCR2 chemokine antagonist, CCR3 chemokine antagonist, CCR5 chemokine antagonist, CD3 antagonist, Chloride channel stimulator, cholesterol solubilizer, CNR1 inhibitor, Cyclin D1 inhibitor, Cytochrome P450 7A1 inhibitor, Cytochrome P450 2E1 (CYP2E1) inhibitor, Diacylglycerol O acyltransferase 1 inhibitor (DGAT1) inhibitor, Diacylglycerol O acyltransferase 1 inhibitor (DGAT2) inhibitor, CXCR4 chemokine antagonist, Dipeptidyl peptidase IV inhibitor, Endosialin modulator, Endothelial nitric oxide synthase stimulator, Eotaxin ligand inhibitor, Extracellular matrix protein modulator, Farnesoid X receptor agonist, Fatty acid synthase inhibitors, FGF1 receptor agonist, Fibroblast activation protein (FAP) inhibitor, Fibroblast growth factor receptor ligands (*e.g.*, FGF-15, FGF-19, FGF-21), Fish oil, Galectin-3 inhibitor, Glucagon receptor agonist, Glucagon-like peptide 1 receptor agonist, Glucocorticoid receptor antagonist, Glucose 6-phosphate 1-dehydrogenase inhibitor, Glutaminase inhibitor, Glutathione precursor, G-protein coupled bile acid receptor 1 agonist, G-protein coupled receptor 84 antagonist, Hedgehog (Hh) modulator, Hepatitis C virus NS3 protease inhibitor, Hepatocyte nuclear factor 4 alpha modulator (HNF4A), Hepatocyte growth factor modulator, Histone deacetylase inhibitor, HMG CoA reductase inhibitor, 11β-Hydroxysteroid dehydrogenase (11β-HSD1) inhibitor, Hypoxia inducible factor-2 alpha inhibitor, IL-1β antagonist, IL-6 receptor agonist, IL-10 agonist, IL-11 antagonist, IL-17 antagonist, Ileal sodium bile acid cotransporter inhibitor, Insulin sensitizer, Insulin ligand agonist, Insulin receptor agonist, integrin modulator, Integrin antagonist intereukin-1 receptor-associated kinase 4 (IRAK4) inhibitor, Jak2 tyrosine kinase inhibitor, Ketohexokinase (KHK) inhibitors, Klotho beta stimulator, leptin, leptin analog, 5-Lipoxygenase inhibitor, Lipoprotein lipase inhibitor, Liver X receptor, LPL gene stimulator, Lysophosphatidate-1 receptor (LPAR-1) antagonist, Lysyl oxidase homolog 2 (LOXL2) inhibitor, LXR inverse agonist, Macrophage mannose receptor 1 modulator, Matrix metalloproteinase (MMPs) inhibitor, MCH receptor-1 antagonist, MEKK-5 protein kinase inhibitor, Membrane copper amine oxidase (VAP-1) inhibitor, Methionine aminopeptidase-2 inhibitor, Methyl CpG binding protein 2 modulator, MicroRNA-132 (miR-132) antagonist, MicroRNA-21(miR-21) inhibitor, Mitochondrial uncoupler, Mixed lineage kinase-3 inhibitor, Myelin basic protein stimulator, NACHT LRR PYD domain protein 3 (NLRP3) inhibitor, NAD-dependent deacetylase sirtuin-1 stimulator, NADPH oxidase inhibitor (NOX), Nicotinic acid receptor 1 agonist, P2X7 purinoceptor modulator, P2Y13

purinoceptor stimulator, PDE 3 inhibitor, PDE 4 inhibitor, PDE 5 inhibitor, PDGF receptor beta modulator, Peptidyl-prolyl cis-trans isomerase A inhibitor, Phenylalanine hydroxylase stimulator, Phospholipase C inhibitor, PPAR alpha agonist, PPAR gamma agonist, PPAR delta agonist, PPAR gamma modulator, PPAR alpha/delta agonist, PPAR alpha/gamma/delta agonist, Protease-activated receptor-2 antagonist, Protein kinase modulator, Rho associated protein kinase 2 (ROCK2) inhibitor, Snitrosoglutathione reductase (GSNOR) enzyme inhibitor, Sodium glucose transporter-2 (SGLT2) inhibitor, SREBP transcription factor inhibitor, STAT-1 inhibitor, STAT-3 modulator, Stearoyl CoA desaturase-1 inhibitor, Snitrosoglutathione reductase (GSNOR) enzyme inhibitor, Suppressor of cytokine signalling-1 stimulator, Suppressor of cytokine signalling-3 stimulator, Spleen tyorosine kinase (SYK) inhibitor, Transforming growth factor β (TGF-β), TGF-β antagonist (*e.g.*, TGF- β1 antagonist, TGF-β2 antagonist, TGF-β3 antagonist, latent TGF β complex modulator), TGF-β receptor antagonist, Transforming growth factor β activated Kinase 1 (TAK1), Thyroid hormone receptor beta agonist, Toll-like receptor (TLR)-4 antagonist, Transglutaminase inhibitor, Tumor necrosis factor alpha (TNFα) ligand inhibitor, Tumor Progression Locus 2 (Tpl2) kinase inhibitor, Tyrosine kinase receptor modulator, GPCR modulator, nuclear hormone receptor modulator, WNT modulators, YAP/TAZ modulator, and Zonulin inhibitor.

[0105] Non-limiting examples of the one or more additional therapeutic agents include:

ACE inhibitors, such as enalapril;

Acetyl CoA carboxylase (ACC) inhibitors, such as NDI-010976 (firsocostat), DRM-01, gemcabene, PF-05175157, QLT-091382 or PF-05221304;

Acetyl CoA carboxylase/Diacylglycerol O acyltransferase 2 inhibitors, such as PF-07055341;

Acetaldehyde dehydrogenase inhibitors, such as ADX-629;

Adenosine receptor agonists, such as CF-102 (namodenoson), CF-101, CF-502, or CGS21680;

Adiponectin receptor agonists, such as ADP-355 or ADP-399;

Amylin/calcitonin receptor agonists, such as KBP-042 or KBP-089;

AMP activated protein kinase stimulators, such as PXL-770 or O-304;

AMP kinase activators/ATP citrate lyase inhibitors, such as as bempedoic acid (ETC-1002, ESP-55016);

AMP activated protein kinase/Endothelial nitric oxide synthase/NAD-dependent deacetylase sirtuin-1 stimulators, such as NS-0200 (leucine + metformin + sildenafil);

Androgen receptor agonists, such as LPCN-1144;

Angiotensin II AT-1 receptor antagonists, such as irbesartan;

Angiopoietin-related protein-3 inhibitors, such as IONIS-ANGPTL3-LRx;

Autotaxin inhibitors, such as PAT-505, PAT-048, GLPG-1690, X-165, PF-8380, AM-063, or BBT-877;

Axl tyrosine kinase receptor inhibitors, such as bemcentinib (BGB-324, R-428);

Bax protein stimulators, such as CBL-514;

Bioactive lipids, such as DS-102;

Cannabinoid receptor type 1 (CNR1) inhibitors, such as namacizumab, GWP-42004, REV-200, or CRB-4001;

Caspase inhibitors, such as emricasan;

Pan cathepsin B inhibitors, such as VBY-376;

Pan cathepsin inhibitors, such as VBY-825;

CCR2/CCR5 chemokine antagonists, such as cenicriviroc, maraviroc, CCX-872, or WXSH-0213;

CCR2 chemokine antagonists, such as propagermanium;

CCR2 chemokine/Angiotensin II AT-1 receptor antagonists, such as DMX-200, or DMX-250;

CCR2/CCR5 chemokine antagonists and FXR agonists, such as LJC-242 (tropifexor + cenivriviroc); CCR3 chemokine antagonists, such as bertilimumab;

Chloride channel stimulators, such as cobiprostone, or lubiprostone;

CD3 antagonists, such as NI-0401 (foralumab);

CXCR4 chemokine antagonists, such as AD-214;

Diglyceride acyltransferase 1 (DGAT1) inhibitors, such as GSK-3008356;

Diacylglycerol O acyltransferase 1 (DGAT1)/Cytochrome P450 2E1 inhibitors (CYP2E1), such as SNP-610;

Diglyceride acyltransferase 2 (DGAT2) inhibitors, such as IONIS-DGAT2Rx, or PF-06865571;

Dipeptidyl peptidase IV inhibitors, such as linagliptin or evogliptin;

Eotaxin ligand inhibitors, such as bertilimumab or CM-101;

Extracellular matrix protein modulators, such as CNX-024;

Farnesoid X receptor (FXR) agonists, such as AGN-242266, AGN-242256, EP-024297, RDX-023, BWL-200, AKN-083, EDP-305, GNF-5120, GS-9674, LMB-763, obeticholic acid, Px-102, Px-103, M790, M780, M450, M-480, MET-409, PX20606, EYP-001, TERN-101, TC-100, INT-2228;

Farnesoid X receptor (FXR)/G-protein coupled bile acid receptor 1(TGR5) agonists, such as INT-767;

Fatty acid synthase inhibitors, such as TVB-2640;

FGF receptor agonists/Klotho beta stimulators, such as BFKB-8488A (RG-7992);

Fibroblast growth factor 19 (rhFGF19)/cytochrome P450 (CYP)7A1 inhibitors, such as NGM-282;

Fibroblast growth factor 21(FGF-21) ligand, such as BMS-986171, BIO89-100, B-1344, or BMS-986036;

Fibroblast growth factor 21(FGF-21)/glucagon like peptide 1 (GLP-1) agonists, such as YH-25723 (YH-25724; YH-22241) or AKR-001;

Fish oil compositions, such as icosapent ethyl (Vascepa®);

Galectin-3 inhibitors, such as GR-MD-02, GB-1107 (Gal-300), or GB1211 (Gal-400);

Glucagon-like peptide 1 receptor (GLP1R) agonists, such as AC-3174, liraglutide, cotadutide (MEDI-0382), exenatide, SAR-425899, LY-3305677, HM-15211, YH-25723, YH-GLP1, RPC-8844, PB-718, or semaglutide;

Glucocorticoid receptor antagonists, such as CORT-118335 (miricorilant);

Glucose 6-phosphate 1-dehydrogenase inhibitors, such as ST001;

G-protein coupled bile acid receptor 1(TGR5) agonists, such as RDX-009 or INT-777;

Heat shock protein 47 (HSP47) inhibitors, such as ND-L02-s0201;

HMG CoA reductase inhibitors, such as atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin;

Hypoxia inducible factor-2 alpha inhibitors, such as PT-2567;

IL-10 agonists, such as peg-ilodecakin;

Ileal sodium bile acid cotransporter inhibitors, such as odevixibat (A-4250), volixibat potassium ethanolate hydrate (SHP-262), GSK2330672, CJ-14199, or elobixibat (A-3309);

Insulin sensitizers, such as, KBP-042, MSDC-0602K, MSDC-5514, Px-102, RG-125 (AZD4076), VVP-100X, CB-4211, or ETI-101;

Insulin ligand/dsInsulin receptor agonists, such as ORMD-0801;

Integrin antagonists, such as IDL-2965;

IL-6 receptor agonists, such as KM-2702;

Ketohexokinase (KHK) inhibitors, such as PF-06835919;

beta Klotho (KLB)- FGF1c agonist, such as MK-3655 (NGM-313);

5-Lipoxygenase inhibitors, such as tipelukast (MN-001), DS-102 (AF-102);

Lipoprotein lipase inhibitors, such as CAT-2003;

LPL gene stimulators, such as alipogene tiparvovec;

Liver X receptor (LXR) modulators, such as PX-L603, PX-L493, BMS-852927, T-0901317, GW-3965, or SR-9238;

Lysophosphatidate-1 receptor antagonists, such as BMT-053011, UD-009 (CP-2090), AR-479, ITMN-10534, BMS-986020, or KI-16198;

Lysyl oxidase homolog 2 inhibitors, such as simtuzumab or PXS-5382A (PXS-5338);

Macrophage mannose receptor 1 modulators, such as tilmanocept-Cy3 (technetium Tc 99m tilmanocept);

Membrane copper amine oxidase (VAP-1) inhibitors, such as TERN-201;

MEKK-5 protein kinase (ASK-1) inhibitors, such as GS-4997, SRT-015, or GS-444217, GST-HG-151;

MCH receptor-1 antagonists, such as CSTI-100 (ALB-127158);

Methionine aminopeptidase-2 inhibitors, such as ZGN-839, ZGN-839, or ZN-1345;

Methyl CpG binding protein 2 modulators, such as mercaptamine;

Mitochondrial uncouplers, such as 2,4-dinitrophenol or HU6;

Mixed lineage kinase-3 inhibitors, such as URMC-099-C;

Myelin basic protein stimulators, such as olesoxime;

NADPH oxidase 1/4 inhibitors, such as GKT-831 or APX-311;

Nicotinic acid receptor 1 agonists, such as ARI-3037MO;

Nitazoxinide;

NACHT LRR PYD domain protein 3 (NLRP3) inhibitors, such as KDDF-201406-03, NBC-6, IFM-514, or JT-194 (JT-349);

Nuclear receptor modulators, such as DUR-928 (DV-928);

P2X7 purinoceptor modulators, such as SGM-1019;

P2Y13 purinoceptor stimulators, such as CER-209;

PDE 3/4 inhibitors, such as tipelukast (MN-001);

PDE 5 inhibitors, such as sildenafil or MSTM-102;

PDGF receptor beta modulators, such as BOT-191 or BOT-509;

Peptidyl-prolyl cis-trans isomerase inhibitors, such as CRV-431 (CPI-432-32), NVP-018, or NV-556 (NVP-025);

Phenylalanine hydroxylase stimulators, such as HepaStem;

PPAR agonists (including PPAR alpha agonists, PPAR alpha/delta agonists, PPAR alpha/delta/gamma agonists, PPAR delta agonists), such as elafibranor (GFT-505), MBX-8025, deuterated pioglitazone R-enantiomer, pioglitazone, DRX-065, saroglitazar, or IVA-337; PPAR alpha agonists, such as aluminum clofibrate, bezafibrate, ciprofibrate, choline fenofibrate, clinofibrate, clofibrate, clofibride, fenofibrate, gemfibrozil, pemafibrate, ronifibrate, simfibrate, an omega-3 fatty acid (fish oil, *e.g.*, icosapent ethyl (Vascepa®), or docosahexaenoic acid), pirinixic acid, GW409544, AZ 242, LY518674, NS-220, AVE8134, BMS-711939, aleglitazar, muraglitzar, or saroglitazar;

PPAR alpha/delta agonists such as elafibranor;

PPAR alpha/delta/gamma agonists such as lanifibranor;

PPAR delta agonists such as seladelpar;

Protease-activated receptor-2 antagonists, such as PZ-235;

Protein kinase modulators, such as CNX-014;

Rho associated protein kinase (ROCK) inhibitors, such as REDX-10178 (REDX-10325) or KD-025;

Semicarbazide-Sensitive Amine Oxidase/Vascular Adhesion Protein-1 (SSAO/VAP-1) Inhibitors, such as PXS-4728A;

S-nitrosoglutathione reductase (GSNOR) enzyme inhibitors, such as SL-891;

Sodium glucose transporter-2 (SGLT2) inhibitors, such as ipragliflozin, remogliflozin etabonate, ertugliflozin, dapagliflozin, tofogliflozin, or sotagliflozin;

SREBP transcription factor inhibitors, such as CAT-2003 or MDV-4463;

Stearoyl CoA desaturase-1 inhibitors, such as aramchol;

Thyroid hormone receptor (THR) beta agonists, such as resmetriom (MGL-3196), MGL-3745, or VK-2809;

TLR-2/TLR-4 antagonists, such as VB-201 (CI-201);

TLR-4 antagonists, such as JKB-121;

Tyrosine kinase receptor modulators, such as CNX-025 or GFE-2137 (repurposed nitazoxanide);

GPCR modulators, such as CNX-023;

Nuclear hormone receptor modulators, such as Px-102;

Xanthine oxidase/Urate anion exchanger 1 (URAT1) inhibitors, such as RLBN-1001, RLBN-1127; and

Zonulin Inhibitors, such as lorazotide acetate (INN-202).

[0106] Additional non-limiting examples of the one or more additional therapeutic agents include:

ACE inhibitors, such as, benazepril, imidapril;

Adenosine A3 receptor antagonists, such as FM-101;

Adropin stimulators, such as RBT-2;

Albumin modulators, such as SYNT-002;

Aldosterone/Mineralocorticoid receptor antagonists, such as MT-3995;

Allogeneic bone marrow-derived mesenchymal stromal cell therapy, such as ORBCEL-M;

Allogenic expanded adipose-derived stem cell therapy, such as Elixcyte™;

AMP activated protein kinase stimulator/Proprotein convertase PC9 inhibitors, such as O-304;

AMP activated protein kinase stimulators, such as DZCY-01, MK-8722, PXL-770;

Angiotensin II AT-1 receptor/CCR2 chemokine antagonists, such as DMX-200;

Angiotensin II AT-2 receptor agonists, such as MOR-107, irbesartan;

Angiotensin II receptor antagonists, such as losartan;

Angiotensinogen ligand inhibitors, such as ALN-AGT;

anti-C1 antibodies, such as BIVV-009 (sutimlimab);

anti-CB1 antibodies, such as GFB-024;

anti-CX3CR1 nanobodies, such as BI-655088;

anti-IL-6 antibodies, such as COR-001;

anti-VEGF-B antibodies, such as CSL-346;

APOA1 gene stimulators/Bromodomain containing protein 2/Bromodomain containing protein 4 inhibitors, such as apabetalone;

Bone morphogenetic protein-7 ligand modulators, such as BMP-7;

Calcium channel inhibitors, such as TBN (xiaotongqin);

Cannabinoid CB1 receptor antagonists, such as JNJ-2463;

CB1 inverse agonists, such as CRB-4001;

Chymase inhibitors, such as fulacimstat (BAY-1142524);

Cyclooxygenase 1 inhibitors, such as GLY-230;

Cyclooxygenase 2/Epoxide hydrolase inhibitors, such as COX-2/soluble epoxide hydrolase;

Cytochrome P450 11B2 inhibitors, such as aldosterone synthase inhibitors;

Ectonucleotide pyrophosphatase-PDE-2 inhibitors, such as BLD-0409;

Endothelin ET-A/Endothelin ET-B receptor antagonists, such as aprocitentan;

Enteropeptidase inhibitors, such as SCO-792;

Erythropoietin receptor antagonists, such as EPO-018B;

Farnesoid X receptor agonists, such as LMB-763;

FGF/PDGF/beta receptor antagonist/p38 MAP kinase inhibitors, such as pirfenidone;

GHR/IGF1 gene inhibitors, such as atesidorsen sodium;

GPR40 agonist/GPR84 antagonists, such as PBI-4050;

G-protein beta subunit inhibitors, such as galleon;

G-protein coupled receptor 84 modulators, such as PBI-4425;

Growth hormone ligand/Growth hormone receptor agonist, such as Jintropin AQ™;

Growth hormone receptor agonists, such as LAT-8881;

Guanylate cyclase receptor agonist/Guanylate cyclase stimulators, such as praliciguat;

Guanylate cyclase stimulators, such as MRL-001, runcaciguat;

Heme oxygenase 1 modulators, such as RBT-1;

HIF prolyl hydroxylase inhibitors, such as TRGX-154;

Insulin sensitizer/Kallikrein 1 modulators, such as DM-199;

Integrin alpha-V/beta-3 antagonists, such as VPI-2690B;

Interleukin 33 ligand inhibitors, such as MEDI-3506;

Kelch like ECH associated protein 1 modulator/Nuclear erythroid 2-related factor 2 stimulators, such as SFX-01;

LDHA gene inhibitors, such as nedosiran;

5-Lipoxygenase activating protein inhibitors, such as AZD-5718;

Lysophosphatidate-1 receptor antagonists, such as BMS-002, EPGN-696;

Matrix extracell phosphoglycoprotein modulator/Phosphatonin receptor agonist, such as TPX-200;

MEKK-5 protein kinase inhibitors, such as selonsertib;

Membrane copper amine oxidase inhibitors, such as UD-014;

Midkine ligand inhibitors, such as CAB-101;

Mineralocorticoid receptor antagonists, such as AZD-9977, esaxerenone, finerenone, KBP-5074;

Myosin 2 inhibitor, such as DeciMab™;

NADPH oxidase 1 inhibitors/NADPH oxidase 4 inhibitors, such as setanaxib;

NADPH oxidase inhibitors, such as APX-115;

NK1 receptor antagonist/Opioid receptor kappa agonist/Opioid receptor mu antagonist, such as AV-104;

Nuclear erythroid 2-related factor 2 stimulator/TGF beta ligand inhibitors, such as CU01-1001;

Nuclear factor kappa B inhibitors, such as mefunidone, bardoxolone methyl (NSC-713200);

PDE 4 inhibitors, such as ART-648, PCS-499;

PDGF receptor beta modulators, such as BOT-191;

PDGF/VEGF receptor antagonists, such as ANG-3070;

PR84 antagonist/GPR40 (FFAR1)/GPR120 (FFAR4) agonist/and a partial activator of peroxisome proliferator-activated receptors (PPAR), such as PBI-4547;

PRKAA2 gene stimulators/AMPK activators, such as PF-06679142, PF-06685249;

Prostacyclin (PGI2) agonists, such as YS-1402;

Protein C activator/Glycoprotein Ib (GPIb) antagonist, such as AB-002;

Protein NOV homolog modulators, such as BLR-200;

Protein tyrosine phosphatase-1B inhibitors, such as MSI-1436;

Reactive oxygen species modulator inhibitors, such as SUL-121;

Renin inhibitors, such as imarikiren hydrochloride;

Rho associated protein kinase 2 inhibitors, such as ANG-4201, RXC-007;

Sodium glucose transporter-2 inhibitors, such as canagliflozin, dapagliflozin propanediol, empagliflozin;

Thromboxane A2 receptor antagonist/Thromboxane synthesis inhibitors, such as SER-150;

Tissue transglutaminase inhibitors, such as ZED-1227;

TRP cation channel C5 inhibitors, such as GFB-887;

TRP cation channel C6 inhibitors, such as ALGX-2224;

Cell adhesion molecule inhibitors, such as glycoside bacterial adhesin antagonists;

Urate anion exchanger 1 (URAT1)/SLC22A12 inhibitors, such as verinurad (RDEA3170);

VIP 1/VIP 2 receptor agonists, such as LBT-3627; and

Xanthine oxidase inhibitors, such as TMX-049, TMX-049DN.

[0107] In some embodiments, the one or more additional therapeutic agents are selected from A-4250, AC-3174, acetylsalicylic acid, AK-20, alipogene tiparvovec, AMX-342, AN-3015, aramchol, ARI-3037MO, ASP-8232, AZD-2693, bertilimumab, Betaine anhydrous, BI-1467335, BMS-986036, BMS-986171, BMT-053011, BOT-191, BTT-1023, CAT-2003, cenicriviroc, CBW-511, CER-209, CF-102, CGS21680, CNX-014, CNX-023, CNX-024, CNX-025, cobiprostone, colesevelam, dapagliflozin, DCR-LIV1, deuterated pioglitazone R-enantiomer, 2,4-dinitrophenol, DRX-065, DS-102, DUR-928, EDP-305, elafibranor (GFT-505), emricasan, enalapril, ertugliflozin, evogliptin, F-351, fluasterone (ST-002), FT-4101, GKT-831, GNF-5120, GRI-0621, GR-MD-02, GS-300, GS-4997, GS-9674, HTD-1801, HST-202, HST-201, hydrochlorothiazide, icosabutate (PRC-4016), icosapent ethyl ester, IMM-124-E, INT-767, INV-240, IONIS-DGAT2Rx, ipragliflozin, Irbesarta, propagermanium, IVA-337, JKB-121, KB-GE-001, KBP-042, KD-025, M790, M780, M450, metformin, sildenafil, LC-280126, linagliptin, liraglutide, LJN-452 (tropifexor), LM-011, LM-002 (CVI-LM-002), LMB-763, LYN-100, MBX-8025, MDV-4463, mercaptamine, MGL-3196, MGL-3745, MP-301, MSDC-0602K, namacizumab, NC-101, NDI-010976, ND-L02-s0201 (BMS-986263), NGM-282, NGM-313, NGM-386, NGM-395, NP-160, norursodeoxycholic acid, NVP-022, O-304, obeticholic acid (OCA), 25HC3S, olesoxime, PAT-505, PAT-048, PBI-4547, peg-ilodecakin, pioglitazone, pirfenidone, PRI-724, PX20606, Px-102, PX-L603, PX-L493, PXS-4728A, PZ-235, RDX-009,

remogliflozin etabonate, RG-125 (AZD4076), RPI-500, saroglitazar, semaglutide, simtuzumab, solithromycin, sotagliflozin, statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin), symbiotic, TCM-606F, TEV-45478,TQA-3526, tipelukast (MN-001), TLY-012, TRX-318, TVB-2640, UD-009, ursodeoxycholic acid, VBY-376, VBY-825, VK-2809, vismodegib, volixibat potassium ethanolate hydrate (SHP-626), VVP-100X, WAV-301, WNT-974, XRx-117, ZGN-839, ZG-5216, ZSYM-008, and ZYSM-007.

[0108] In some embodients, the methods and pharmaceutical compositions provided herein include a therapeutically effective amount of an Apoptosis Signal-Regulating Kinase 1 (ASK1) inhibitor and a therapeutically effective amount of an LPAR1 antagonist, wherein the LPAR1 antagonist is a compound of Compounds 1-13 provided herein or pharmaceutically acceptable salt thereof.

[0109] In some embodiments of the methods and pharmaceutical compositions disclosed herein, the ASK1 inhibitor is GS-4997 (selonsertib, SEL).

[0110] ASK1 inhibitors can be synthesized and characterized using methods known to those of skill in the art, such as those described in U.S. 2007/0276050, U.S. 2011/0009410, and U.S. 2013/0197037.

[0111] In some embodients, the methods and pharmaceutical compositions provided herein include a therapeutically effective amount of an Acetyl-CoA Carboxylase (ACC) inhibitor and a therapeutically effective amount of an LPAR1 antagonist, wherein the LPAR1 antagonist is a compound of Compounds 1-13 provided herein or pharmaceutically acceptable salt thereof.

[0112] In some embodiments of the methods and pharmaceutical compositions disclosed herein, the ACC inhibitor is GS-0976 (firsocostat, FIR).

[0113] ACC inhibitors can be synthesized and characterized using methods known to those of skill in the art, such as those described in U.S. Patent No. 9,453,026 and U.S. Patent No. 10,183,951.

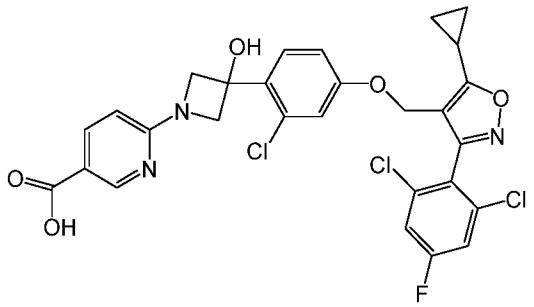
[0114] In some embodiments, the methods and compositions provided herein include a therapeutically effective amount of a PPAR agonist (*e.g.*, PPAR alpha agonist, PPAR alpha/delta agonist, PPARalpha/delta/gamma agonist, PPAR delta agonist) or fish oil, a therapeutically

effective amount of an Acetyl CoA Carboxylase (ACC) inhibitor, such as GS-0976 (firsocostat, FIR), and a therapeutically effective amount of an LPAR1 antagonist, wherein the LPAR1 antagonist is a compound of Compounds 1-13 provided herein or pharmaceutically acceptable salt thereof. In some embodiments, the PPAR agonist is a PPAR alpha agonist. In some embodiments, the PPAR alpha agonist is selected from aluminum clofibrate, bezafibrate, ciprofibrate, choline fenofibrate, clinofibrate, clofibrate, clofibride, fenofibrate, gemfibrozil, pemafibrate, ronifibrate, simfibrate, pirinixic acid, GW409544, AZ 242, LY518674, NS-220, AVE8134, BMS-711939, aleglitazar, muraglitzar, and saroglitazar. In some embodiments, the PPAR agonist (*e.g.*, PPAR alpha agonist) is a fibrate. In some embodiments, the PPAR agonist (*e.g.*, PPAR alpha agonist) is fenofibrate. In some embodiments, the PPAR agonist is a PPAR alpha/delta agonist (*e.g.*, elafibranor). In some embodiments, the PPAR agonist is a PPAR alpha/delta/gamma agonist (*e.g.*, lanifibranor). In some embodiments, the PPAR agonist is a PPAR delta agonist (*e.g.*, seladelpar). In some embodiments the fish oil is an omega-3 fatty acid or docosahexaenoic acid. In some embodiments, the fish oil is icosapent ethyl (*e.g.*, Vascepa®).

[0115] In some embodiments, the methods and compositions provided herein include a therapeutically effective amount of a Farnesoid X Receptor (FXR) agonist and a therapeutically effective amount of an LPAR1 antagonist, wherein the LPAR1 antagonist is a compound of Compounds 1-13 provided herein or pharmaceutically acceptable salt thereof.

[0116] In some embodiments of the methods and pharmaceutical compositions disclosed herein, the FXR agonist is GS-9674 (cilofexor, CILO).

[0117] In some embodiments of the methods and pharmaceutical compositions disclosed herein, the FXR agonist is a compound having the structure:



or a pharmaceutically acceptable salt thereof.

[0118] In some embodiments, the methods and compositions provided herein include a therapeutically effective amount of a GLP-1 receptor agonist and a therapeutically effective amount of an LPAR1 antagonist, wherein the LPAR1 antagonist is a compound of Compounds 1-13 provided herein or a pharmaceutically acceptable salt thereof. In some embodiments, the GLP-1 receptor agonist is liraglutide or semaglutide. In some embodiments, the GLP-1 receptor agonist is semaglutide.

[0119] In some embodiments, the methods and compositions provided herein include a therapeutically effective amount of a TGFβ antagonist and a therapeutically effective amount of an LPAR1 antagonist, wherein the LPAR1 antagonist is a compound of Compounds 1-13 provided herein or pharmaceutically acceptable salt thereof. In some embodiments, the TGFβ antagonist is a TGFβ -specific antibody. TGFβ -specific antibodies can be prepared and characterized using methods known to those of skill in the art, such as those described in PCT International Application Publication No. WO 2018/129329 and in U.S. Patent No. 9,518,112. In some embodiments, the TGFβ antagonist binds to a TGFβ latency-associated peptide (LAP), *e.g.*, TGFβ 1-LAP. TGFβ 1-LAP-specific antibodies can be prepared and characterized using methods known to those of skill in the art, such as those described in U.S. Patent No. 8,198,412 or U.S. Patent No. 10,017,567. In some embodiments, the TGFβ antagonist binds to TGFβ (*e.g.*, TGFβ 1) in a context independent manner (*e.g.*, independent of the presentation of TGF β in a specific tissue or organ). In some embodiments, the TGFβ antagonist binds to TGFβ (*e.g.*, TGFβ 1) in a context-dependent manner. In some embodiments, the TGFβ antagonist blocks activation of latent TGFβ (*e.g.*, latent TGFβ 1) that is localized in extracellular matrix, *e.g.*, in connective tissue of the liver. In some embodiments, the TGFβ antagonist blocks activation of latent TGFβ (*e.g.*, latent TGFβ 1) that is localized in the thymus, a lymph node, or in a tumor microenvironment (*e.g.*, in a patient having liver cancer). In some embodiments, the TGFβ antagonist blocks activation of latent TGFβ (*e.g.*, latent TGFβ 1) by Latent TGFβ Binding Protein (LTBP). In some embodiments, the TGFβ antagonist blocks activation of latent TGFβ (*e.g.*, latent TGFβ 1) by Glycoprotein-A Repetitions Predominant protein (GARP), as described, *e.g.*, in U.S. Patent No. 10,000,572. In some embodiments, the TGFβ antagonist is ARGX-115. In some embodiments, the TGFβ antagonist is an anti-latency-associated peptide (LAP) antibody that specifically binds to a LAP-TGFβ complex. In some embodiments, the anti-LAP antibody specifically binds to LAP-TGFβ complexes in extracellular matrix (ECM), *e.g.*, of connective tissue in the liver. In

some embodiments, the anti-LAP antibody specifically binds to LAP-TGFβ complexes on the surfaces of certain immunosuppressive cell types, such as regulatory T cells (Tregs), tumor-associated macrophages, or myeloid-derived suppressor cells, *e.g.*, in a tumor microenvironment. In some embodiments, the anti-LAP antibody is a TLS-01 antibody. In some embodiments, the anti-LAP antibody specifically binds to LAP-TGFβ complexes in any context. In some embodiments, the anti-LAP antibody is a TLS-02 antibody. In some embodiments, the TGFβ antagonist comprises a TGFβ receptor. In some embodiments, the TGFβ antagonist is a TGFβ receptor-Fc fusion protein. In some embodiments, the TGFβ antagonist is an antibody comprising a TGFβ receptor. TGFβ antagonists comprising a TGFβ receptor that can be useful in connection with the compositions and methods provided herein have been described, *e.g.*, in PCT International Publication Nos. WO 2019/113123 A1 and WO 2019/113464 A1.

[0120] In some embodiments the methods and compositions provided herein include a therapeutically effective amount of an LPAR1 antagonist and of an additional therapeutic agent selected from an ACE inhibitor, adenosine A3 receptor antagonist, adropin stimulator, albumin modulator, aldosterone antagonist, AMP activated protein kinase stimulator, angiotensin II AT-2 receptor agonist, angiotensin II receptor antagonist, angiotensinogen ligand inhibitor, APOA1 gene stimulator, apolipoprotein L1 modulator, bone morphogenetic protein-7 ligand modulator, bromodomain containing protein 2 inhibitor, bromodomain containing protein 4 inhibitor, calcium channel inhibitors, cannabinoid CB1 receptor antagonists, CB1 inverse agonists, CCR2 chemokine antagonist, chymase inhibitor, complement C1s subcomponent inhibitor, CX3CR1 chemokine antagonist, cyclooxygenase 1 inhibitor, cyclooxygenase 2 inhibitor, cytochrome P450 11B2 inhibitor, ectonucleotide pyrophosphatase-PDE-2 inhibitor, endothelin ET-A receptor antagonist, endothelin ET-B receptor antagonist, enteropeptidase inhibitor, epoxide hydrolase inhibitor, erythropoietin receptor antagonist, farnesoid X receptor agonist, FGF receptor antagonists, free fatty acid receptor 1 agonist, GHR gene inhibitor, glycoprotein Ib (GPIb) antagonist, GPR40 agonist, GPR84 antagonist, G-protein beta subunit inhibitor, G-protein coupled receptor 120 agonist, G-protein coupled receptor 84 modulator, growth hormone ligand, growth hormone receptor agonist, guanylate cyclase receptor agonists, guanylate cyclase stimulator, heme oxygenase 1 modulator, HIF prolyl hydroxylase inhibitor, IGF1 gene inhibitors, IgG receptor FcRn large subunit p51 modulator, IL-6 receptor antagonist, integrin alpha-V/beta-3 antagonist, interleukin 33 ligand inhibitor, Kelch-like ECH associated protein 1 modulator,

LDHA gene inhibitor, 5-lipoxygenase activating protein inhibitor, lysophosphatidate-1 receptor antagonist, matrix extracellular phosphoglycoprotein modulator, membrane copper amine oxidase inhibitor, midkine ligand inhibitor, mineralocorticoid receptor antagonist, myosin 2 inhibitors, NADPH oxidase 1 inhibitor, NADPH oxidase 4 inhibitor, NADPH oxidase inhibitor, NK1 receptor antagonist, nuclear erythroid 2-related factor 2 stimulator, nuclear factor kappa B inhibitor, opioid receptor kappa agonist, opioid receptor mu antagonists p38 MAP kinase inhibitor, PDE4 inhibitor, PDGF receptor antagonist, PDGF receptor beta modulator, phosphatonin receptor agonist, PRKAA2 gene stimulator, proprotein convertase PC9 inhibitor, prostacyclin (PGI2) agonist, protein C activator, protein NOV homolog modulator, protein tyrosine phosphatase-1B inhibitor, reactive oxygen species modulator inhibitor, renin inhibitor, Rho associated protein kinase 2 inhibitor, SLC22A12 inhibitor, sodium glucose transporter-2 inhibitor, solute carrier family inhibitor, TGF beta ligand inhibitor, TGF beta receptor antagonist, thromboxane A2 receptor antagonist, thromboxane synthesis inhibitor, tissue transglutaminase inhibitor, TRP cation channel C5 inhibitor, TRP cation channel C6 inhibitor, tryptophanase inhibitor, unspecified cell adhesion molecule inhibitor, urate anion exchanger 1 inhibitor, vasopressin V1a receptor antagonist, VEGF receptor antagonist, VIP 1 receptor agonist, VIP 2 receptor agonist, and Xanthine oxidase inhibitor.

[0121] In some embodiments the methods and compositions provided herein include a therapeutically effective amount of an LPAR1 antagonist and of an additional therapeutic agent selected from a VEGFR inhibitor, a FGFR inhibitor, a PDGFR inhibitor, an autaxin inhibitor, a GPR84 agonist, a PASK inhibitor, a CFTR agonist, a JAK1 inhibitor, an ADAMTS5 inhibitor, a TOL2/3 inhibitor, a CTGF inhibitor, a soluble PTX2, an anti-galectin-3 antibody, an integrin-α_V-β_6/α_V-β_1 antagonist, a JNK1 inhibitor, a mineralocorticoid receptor antagonist, a Nrf2 activator, a chymase inhibitor, a PDE inhibitor, a NOX1/4 inhibitor, a leukotriene/thromboxane receptor antagonist, SLC22A12 inhibitor, an sGC inhibitor, and a xanthine oxidase inhibitor.

[0122] In some embodiments the methods and compositions provided herein include a therapeutically effective amount of an LPAR1 antagonist and of an additional therapeutic agent selected from nintedanib, pirfenidone, pamrevlumab, PRM-151, GB-0139, PLN-74809, CC-90001, finerenone, BAY1142524, PCS-499, setanaxib, SER150, RDEA3170, praliciguat, TMX-049, GLPG1690, GLPG1205, GLPG1972, GLPG4059, GLPG2737, GLPG3970, and filgotinib.

[0123] In some embodiments the methods and compositions provided herein include a therapeutically effective amount of an LPAR1 antagonist and of an additional therapeutic agent selected from A-717, ACF-TEI, alanyl-glutamine, ALLN-346, anti-SCF248 antibody, anti-TAGE monoclonal antibodies, anti-TGF beta antibodies, AST-120, BAY-2327949, BI-685509, DP-001, DZ-4001, GDT-01, LNP-1892, MEDI-8367, microRNA-targeting antisense oligonucleotide therapy, MK-2060, MPC-300-IV, NAV-003, Neo-Kidney Augment™ (NKA), NP-135, NP-160, NP-251, NRF-803, PBI-4610, PHN-033, R-HSC-010, salvianolic acid, SGF-3, SPD-01, Sugaheal variant, SZ-005, TCF-12, UMC119-06, VAR-400, veverimer, VS-105, and XRx-221.

EXAMPLES

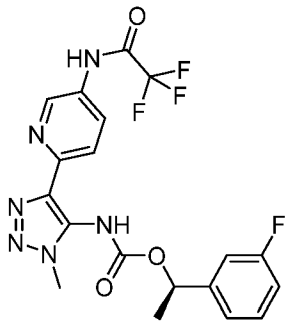
[0124] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that these examples are exemplary and not exhaustive. Many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

[0125] Compounds disclosed herein can be prepared according to the procedures of the following Examples, using appropriate materials and are further exemplified by the following specific examples. The examples further illustrate details for the preparation of the compounds of the present disclosure. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. For synthesizing compounds which are embodiments described in the present disclosure, inspection of the structure of the compound to be synthesized will provide the identity of each substituent group. In some cases, the identity of the final product can render apparent the identity of the necessary starting materials by a process of inspection, given the examples herein. Compounds can be isolated in the form of their pharmaceutically acceptable salts, such as those described above. Compounds described herein are typically stable and isolatable at room temperature and pressure.

[0126] An illustration of the preparation of compounds disclosed herein is shown below. Unless otherwise indicated, variables have the same meaning as described above. The examples

presented below are intended to illustrate particular embodiments of the disclosure. Suitable starting materials, building blocks and reagents employed in the synthesis as described below are commercially available from AbovChem, Acros Organics, Astatech, Combi Blocks, Oakwood Chemical, or Sigma-Aldrich, for example, or can be routinely prepared by procedures described in the literature, for example in "March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 5th Edition; John Wiley & Sons or T. Eicher, S. Hauptmann "The Chemistry of Heterocycles; Structures, Reactions, Synthesis and Application", 2nd edition, Wiley-VCH 2003; Fieser et al. "Fiesers´ Reagents for organic Synthesis" John Wiley & Sons 2000.

Example 1: ***<u>Preparation of (R)-1-(3-fluorophenyl)ethyl (1-methyl-4-(5-(2,2,2-trifluoroacetamido)pyridin-2-yl)-1H-1,2,3-triazol-5-yl)carbamate (Compound 1)</u>***



Compound 1

***Step 1*: 4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (*Intermediate 1*)**

[0127] 4-bromo-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (50 mmol) was dissolved in 500 mL of tetrahydrofuran and submerged in a –78 °C bath for 15 minutes. A 1 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (54 mmol) was dropwise over 15 minutes. A 2.5 M solution of n-butyllithium (105 mmol) in hexanes was added dropwise over 20 minutes and allowed to stir for an additional 1 hour. A 1.9 M solution of zinc chloride (105 mmol) in 2-methyl tetrahydrofuran was added dropwise over 15 minutes. The reaction mixture was warmed to ambient temperature by submerging in a water bath and allowed to stir for 30 minutes. The resulting mixture was sparged with argon gas for 10 min, and then *tert*-butyl (6-bromopyridin-3-yl)carbamate (50 mmol) and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (5 mmol) were added. The reaction was

heated at 75 °C for 3 hours, and then cooled to ambient temperature. The reaction was diluted with 350 mL of a 2 M aqueous solution of sodium hydroxide and 300 mL of diethyl ether. The aqueous layer was separated, and the organic layer was extract with a 1 M aqueous solution of sodium hydroxide (100 mL). The combined aqueous layer was washed with a 1:1 mixture of ethyl acetate and diethyl ether (150 mL × 2). 80 mL of concentrated hydrochloric acid was dropwise over 10 min under vigorous stirring to adjust pH to 4. The mixture was filtered, and the filter cake was washed with water (100 mL) and a 1:1 mixture of ethyl acetate and diethyl ether (100 mL x 2). The precipitate was dried under reduced pressure to provide 4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 1***).

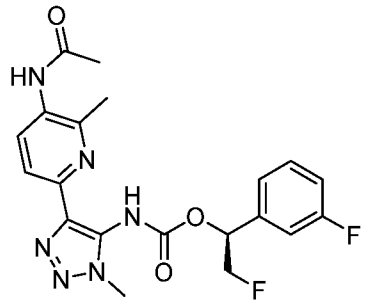
Step 2: 5-(5-amino-2-pyridyl)-3-methyl-triazole-4-carboxylic acid, trifluoroacetic acid salt (Intermediate 2)

[0128] A mixture of 4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (0.27 mmol) in dichloromethane (3 mL) was treated with trifluoroacetic acid (1.0 mL, 13 mmol), and the mixture was stirred at room temperature for 1 hour. After completion of the reaction, the solution was concentrated *in vacuo* to provide 5-(5-amino-2-pyridyl)-3-methyl-triazole-4-carboxylic acid, trifluoroacetic acid salt (***Intermediate 2***).

Step 3: (R)-1-(3-fluorophenyl)ethyl (1-methyl-4-(5-(2,2,2-trifluoroacetamido)pyridin-2-yl)-1H-1,2,3-triazol-5-yl)carbamate (Compound 1)

[0129] To a mixture of 5-(5-amino-2-pyridyl)-3-methyl-triazole-4-carboxylic acid, trifluoroacetic acid salt (***Intermediate 2***, 96 μmol), 1-propanephosphonic acid cyclic anhydride (50% in THF, 0.24 mmol), and azidotrimethysilane (0.24 mmol) acid in THF (1 mL) was added triethylamine (0.38 mmol) dropwise followed by (1*R*)-1-(3-fluorophenyl)ethanol (0.13 mmol) . The reaction mixture was heated at 80°C for 2 hours, cooled to room temperature, concentrated, and purified by silica gel chromatography to provide (*R*)-1-(3-fluorophenyl)ethyl (1-methyl-4-(5-(2,2,2-trifluoroacetamido)pyridin-2-yl)-1*H*-1,2,3-triazol-5-yl)carbamate (***Compound 1***). (MS (*m/z*) 453.1 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.88 (s, 1H), 8.18 (dd, *J* = 8.7, 2.6 Hz, 1H), 8.01 – 7.91 (m, 1H), 7.36 (m, 1H), 7.31 - 7.08 (m, 2H), 7.03 (t, *J* = 8.6 Hz, 1H), 5.82 (m, 1H), 3.98 (s, 3H), 1.51 (m, 3H).

Example 2: Preparation of (S)-2-fluoro-1-(3-fluorophenyl)ethyl (4-(5-acetamido-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 2)



Compound 2

Step 1: 4-(5-((tert-butoxycarbonyl)amino)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (Intermediate 3)

[0130] Following the procedure described in example above for the synthesis of 4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 1***), 4-(5-((*tert*-butoxycarbonyl)amino)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 3***) was prepared by replacing *tert*-butyl (6-bromopyridin-3-yl)carbamate with *tert*-butyl (6-bromo-2-methylpyridin-3-yl)carbamate.

Step 2: tert-butyl (S)-(6-(5-(((2-fluoro-1-(3-fluorophenyl)ethoxy)carbonyl)carbamoyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)carbamate (Intermediate 4)

[0131] 4-(5-((*tert*-butoxycarbonyl)amino)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 3***, 1.6 mmol), azidotrimethylsilane (2.3 mmol), and T3P (50% in THF) (2.3 mmol) were dissolved in THF (6 mL). Triethylamine (4.7 mmol) was added dropwise at RT resulting in a clear solution after 5-30 minutes. (*S*)-2-fluoro-1-(3-fluorophenyl)ethan-1-ol (3.2 mmol) was added and the reaction was heated at 70 °C for 1-2 h. After cooling, water and ethyl acetate were added, and layers were separated. The organic phase was concentrated under reduced pressure and then the residue was purified by column chromatography to afford *tert*-butyl (S)-(6-(5-(((2-fluoro-1-(3-fluorophenyl)ethoxy)carbonyl) carbamoyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)carbamate (***Intermediate 4***).

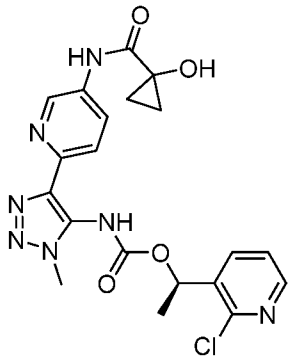
Step 3: (S)-2-fluoro-1-(3-fluorophenyl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carbonyl)carbamate hydrochloride (Intermediate 5)

[0132] *tert*-butyl (S)-(6-(5-(((2-fluoro-1-(3-fluorophenyl)ethoxy)carbonyl)carbamoyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)carbamate (***Intermediate 4***) was suspended in hydrogen chloride solution (10 mL, 4M in dioxanes) for 1 h. The mixture was then concentrated *in vacuo* to afford (S)-2-fluoro-1-(3-fluorophenyl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carbonyl)carbamate hydrochloride (***Intermediate 5***), which was used without further purification.

Step 4: (S)-2-fluoro-1-(3-fluorophenyl)ethyl (4-(5-acetamido-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 2)

[0133] A solution of (S)-2-fluoro-1-(3-fluorophenyl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carbonyl)carbamate hydrochloride (***Intermediate 5***, 67 μmol) in 1 mL DCM was treated with pyridine (0.2 mL). Acetyl chloride (0.14 mmol) was added and the mixture was stirred at room temperature. After 30 minutes, the reaction was concentrated and dissolved in tetrahydrofuran (2 mL) and 1 M aqueous sodium hydroxide solution (2 mL) and stirred vigorously for 10 minutes. The reaction was quenched with sat. ammonium chloride and extracted with ethyl acetate (2x 10 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by RP HPLC to provide (*S*)-2-fluoro-1-(3-fluorophenyl)ethyl (4-(5-acetamido-6-methylpyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Compound 2***). (MS (*m/z*) 431.4 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.07 – 7.75 (m, 2H), 7.61 – 7.45 (m, 1H), 7.34 (dd, *J* = 17.3, 8.8 Hz, 2H), 7.17 (td, *J* = 8.4, 2.5 Hz, 1H), 6.01 (t, *J* = 8.2 Hz, 1H), 4.48 (t, *J* = 8.5 Hz, 1H), 4.19 (t, *J* = 8.0 Hz, 1H), 4.06 (s, 3H), 2.37 (s, 3H), 2.18 (s, 3H).

Example 3: (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 3)



Compound 3

Step 1: (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-((tert-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Intermediate 6)

[0134] To a mixture of 4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 1***, 9.4 mmol), 1-propanephosphonic acid cyclic anhydride (50% in THF, 14.1 mmol), and azidotrimethysilane (14.1 mmol) acid in THF (100 mL) was added triethylamine(23.5 mmol) dropwise. The reaction mixture was heated at 70°C for 1 hour followed by addition of (R)-1-(2-chloropyridin-3-yl)ethan-1-ol (18.8 mmol) at the same temperature. After heating for 24 hours, the reaction was cooled to room temperature, concentrated and purified by silica gel chromatography to provide (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Intermediate 6***). (MS (*m/z*) 474.12 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.67 (s, 1H), 8.31 (s, 1H), 8.08 (s, 1H), 7.94 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.84 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.47 (s, 1H), 6.07 (d, *J* = 6.7 Hz, 1H), 3.98 (s, 3H), 1.75 – 1.46 (m, 12H).

Step 2: Preparation of (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Intermediate 7)

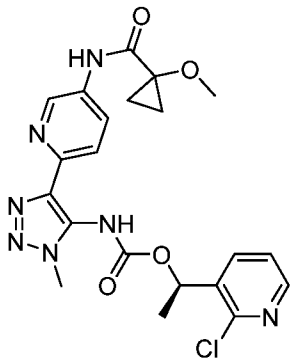
[0135] 4 M HCl in 1,4-dioxane (20 mL) was added to (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Intermediate 6***, 6.9 mmol). The resulting suspension was stirred for 18 hours at room temperature. The reaction was concentrated to afford (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-

aminopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate as the hydrochloride salt (***Intermediate 7***).

Step 3: Preparation of (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 3)

[0136] To a mixture of (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 7***) (0.060 mmol) in pyridine (0.5 mL) was added 1-hydroxycyclopropanecarboxylic acid (0.064 mmol) and N-Ethyl-N′-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.091 mmol). The reaction mixture was left with magnetic stirring for 2 hours at which point water (1 mL) was added, and the mixture was concentrated under reduced pressure. The residue was subjected to purification by RP-HPLC to provide (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Compound 3***). (MS (*m/z*) 458.2 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.92 (s, 1H), 8.55 – 7.75 (m, 4H), 7.47 (s, 1H), 6.08 (q, J = 6.4 Hz, 1H), 3.99 (s, 3H), 1.61 (s, 3H), 1.42 – 1.25 (m, 2H), 1.20 – 1.03 (m, 2H).

<u>Example 4: (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-methoxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 4)</u>

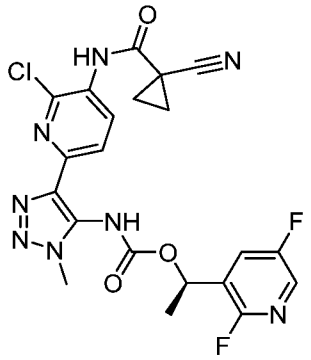


Compound 4

[0137] The title compound (***Compound 4***) was prepared analogously to Example 3 (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Compound 3***) by substituting 1-methoxycyclopropane-carboxylic acid for 1-hydroxycyclopropanecarboxylic acid in step 3. (MS (*m/z*) 467.1 $[M+H]^+$).

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.92 (s, 1H), 8.49 – 7.79 (m, 4H), 7.47 (s, 1H), 6.23 – 5.88 (m, 1H), 3.99 (s, 3H), 3.47 (s, 3H), 1.61 (s, 3H), 1.38 – 1.31 (m, 2H), 1.27 – 1.19 (m, 2H).

Example 5: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(6-chloro-5-(1-cyanocyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 5)



Compound 5

Step 1: Preparation of tert-butyl N-(6-bromo-2-chloro-3-pyridyl)carbamate (Intermediate 8)

[0138] A 50-mL round bottom flask, fitted with a stir bar, was charged with 6-bromo-2-chloro-pyridin-3-amine (4.8 mmol) and tetrahydrofuran (10 mL). The solution was placed under an atmosphere of argon and cooled to - 5 °C. A 1 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (54 mmol) was added dropwise and allowed to stir for 10 min. Di-*tert*-butyl dicarbonate (6.3 mmol) was then added dropwise as a solution in THF (10 mL), and the solution was allowed to warm to room temperature. Acetic acid (15 mmol) was then added along with 15 mass equivalents of silica. The crude mixture was concentrated to dryness and purified by silica gel column chromatography to provide the title intermediate.

Step 2: Preparation of 5-[5-(tert-butoxycarbonylamino)-6-chloro-2-pyridyl]-3-methyl-triazole-4-carboxylic acid (Intermediate 9)

[0139] The title intermediate was prepared according to the procedure that provided 4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 1***) by substituting *tert*-butyl *N*-(6-bromo-2-chloro-3-pyridyl)carbamate for *tert*-butyl (6-bromopyridin-3-yl)carbamate (50 mmol) and chloro(2-dicyclohexylphosphino-2',4',6'-

triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) for [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane.

Step 3: Preparation of (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-((tert-butoxycarbonyl) amino)-6-chloropyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carbonyl)carbamate (Intermediate 10)

[0140] The title intermediate was prepared via a procedure analogous to that which provided *tert*-butyl (*S*)-(6-(5-(((2-fluoro-1-(3-fluorophenyl)ethoxy)carbonyl)carbamoyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)carbamate (***Intermediate 4, Example 2, step 2***) in which 5-[5-(*tert*-butoxycarbonylamino)-6-chloro-2-pyridyl]-3-methyl-triazole-4-carboxylic acid (***Intermediate 9***) replaced 4-(5-((*tert*-butoxycarbonyl)amino)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 3***) and (1R)-1-(2,5-difluoro-3-pyridyl)ethanol replaced (*S*)-2-fluoro-1-(3-fluorophenyl)ethan-1-ol.

Step 4: Preparation of [(1R)-1-(2,5-difluoro-3-pyridyl)ethyl] N-[5-(5-amino-6-chloro-2-pyridyl)-3-methyl-triazol-4-yl]carbamate hydrochloride (intermediate 11)

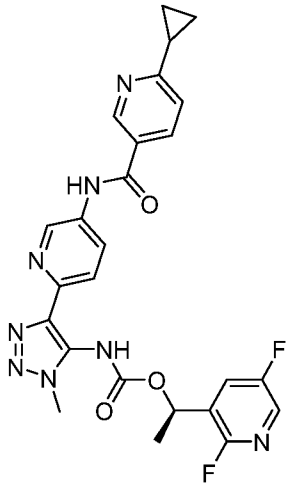
[0141] The title intermediate was furnished by the same procedure (HCl/dioxanes) that was used to provide (*S*)-2-fluoro-1-(3-fluorophenyl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1*H*-1,2,3-triazole-5-carbonyl)carbamate hydrochloride (***Intermediate 5, Example 2, step 3***).

Step 5: Preparation of (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(6-chloro-5-(1-cyanocyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 5)

[0142] The title example was prepared analogously to (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Compound 3***) by substituting [(1*R*)-1-(2,5-difluoro-3-pyridyl)ethyl] *N*-[5-(5-amino-6-chloro-2-pyridyl)-3-methyl-triazol-4-yl]carbamate hydrochloride (***Intermediate 11***) for (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 7***) and 1-cyanocyclopropanecarboxylic acid for 1-hydroxycyclopropanecarboxylic acid. (MS (*m/z*) 502.9 $[M+H]^+$). ^1H NMR (400 MHz,

Methanol-d_4) δ 8.37 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.4 Hz, 3H), 6.00 (d, J = 7.6 Hz, 1H), 4.00 (s, 3H), 1.87 – 1.37 (m, 7H).

Example 6: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(6-cyclopropylnicotinamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 6)



Compound 6

Step 1: tert-butyl (R)-(6-(5-(((1-(2,5-difluoropyridin-3-yl)ethoxy)carbonyl)amino)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)carbamate (Intermediate 12)

[0143] To a mixture of 4-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)-1-methyl-1H-1,2,3-triazole-5-carboxylic acid (***Intermediate 1***, 10.6 mmol), 1-propanephosphonic acid cyclic anhydride (50% in THF, 16 mmol), and azidotrimethysilane (16 mmol) acid in THF (15 mL) was added triethylamine (27 mmol) dropwise. The reaction mixture was heated at 70°C for 0.5 hour followed by addition of (R)-1-(2,5-difluoropyridin-3-yl)ethan-1-ol (21 mmol) at the same temperature. After heating for 24 hours, the reaction was cooled to room temperature, concentrated and purified by silica gel chromatography to provide *tert*-butyl (*R*)-(6-(5-(((1-(2,5-difluoropyridin-3-yl)ethoxy)carbonyl)amino)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)carbamate.

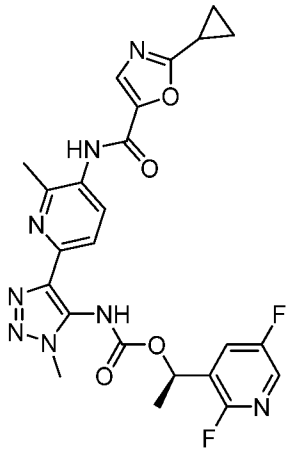
Step 2: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Intermediate 13)

[0144] 4 M HCl in 1,4-dioxane (15 mL) was added to *tert*-butyl (*R*)-(6-(5-(((1-(2,5-difluoropyridin-3-yl)ethoxy)carbonyl)amino)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)carbamate (4.2 mmol). The resulting suspension was stirred for 18 hours at room temperature. The reaction was concentrated to afford (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 13***).

Step 3: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(6-cyclopropylnicotinamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 6)

[0145] The title example was prepared analogously to (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Compound 3***) by substituting (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 13***) for (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 7***) and 6-cyclopropylpyridine-3-carboxylic acid for 1-hydroxycyclopropanecarboxylic acid. (MS (*m/z*) 521.0 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 – 8.83 (m, 2H), 8.23 (ddd, *J* = 8.3, 6.1, 2.5 Hz, 2H), 8.16 – 7.61 (m, 3H), 7.41 (dd, *J* = 8.3, 0.8 Hz, 1H), 5.96 (d, *J* = 6.7 Hz, 1H), 4.00 (s, 3H), 2.22 (tt, *J* = 8.0, 5.1 Hz, 1H), 1.62 (s, 3H), 1.12 (ddt, *J* = 12.2, 7.5, 2.6 Hz, 4H).

Example 7: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-cyclopropyloxazole-5-carboxamido)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 7)



Compound 7

Step 1: Preparation of (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-((tert-butoxycarbonyl) amino)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Intermediate 14)

[0146] In a manner analogous to the preparation of *tert*-butyl (*S*)-(6-(5-(((2-fluoro-1-(3-fluorophenyl)ethoxy)carbonyl)carbamoyl)-1-methyl-1H-1,2,3-triazol-4-yl)-2-methylpyridin-3-yl)carbamate (***Intermediate 4, Example 2, step 2***), the title intermediate was prepared by replacing (*S*)-2-fluoro-1-(3-fluorophenyl)ethan-1-ol with (*R*)-1-(2,5-difluoropyridin-3-yl)ethan-1-ol.

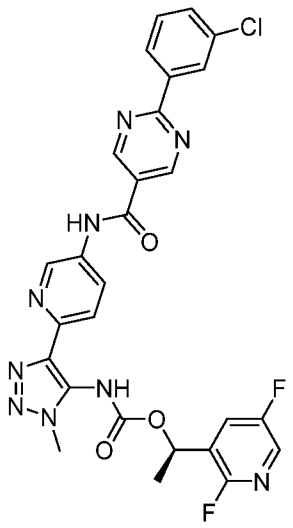
Step 2: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate hydrochloride (Intermediate 15)

[0147] (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-((*tert*-butoxycarbonyl)amino)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (***Intermediate 14***) was suspended in hydrogen chloride solution for 1 h. The mixture was then concentrated *in vacuo* to afford (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 15***), which was used without further purification.

Step 3: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-cyclopropyloxazole-5-carboxamido)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 7)

[0148] The title example was prepared analogously to (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 3, step 3***) by replacing (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 7***) with (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 15***) and 1-hydroxycyclopropane carboxylic acid with 2-cyclopropyloxazole-5-carboxylic acid. (MS (*m/z*) 521.0 $[M+H]^+$). ^1H NMR (400 MHz, Methanol-d_4) δ 8.04 (bs, 1H), 7.92 – 7.82 (m, 2H), 7.75 (s, 1H), 5.98 (m, 1H), 4.02 (s, 3H), 2.50 (s, 3H), 2.25 (p, J = 6.7 Hz, 1H), 1.61 (bs, 3H), 1.23 (m, 4H).

Example 8: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-(3-chlorophenyl)pyrimidine-5-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate *(Compound 8)*



Compound 8

Step 1: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-chloropyrimidine-5-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Intermediate 16)

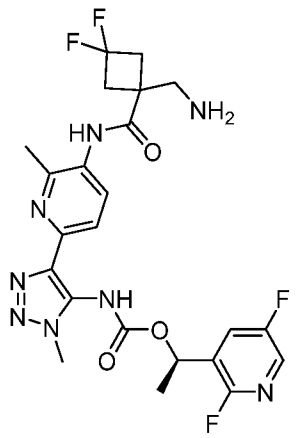
[0149] The title intermediate was prepared from (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 13***)

analogously to (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(6-cyclopropylnicotinamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 6, step 3***) by substituting 2-chloro pyrimidine-5-carboxylic acid for 6-cyclopropylpyridine-3-carboxylic acid.

Step 2: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-(3-chlorophenyl)pyrimidine-5-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 8)

[0150] A vial, fitted with a stir bar, was charged with (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-chloropyrimidine-5-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Intermediate 16***, 97 µmol), (3-chlorophenyl)boronic acid (145 µmol, 1.5 eq), tetrakis(triphenylphosphine)palladium(0) (9.7 µmol, 10 mol%), and potassium carbonate (290 µmol, 3.0 eq). 1,4-Dioxane (2 mL) and distilled water (0.2 mL) were added by syringe, and the mixture was de-gassed by bubbling argon through for 5 min while mixing. The vial was sealed with a septum cap and the mixture heated to 90 °C. Upon complete consumption of starting material, a saturated solution of sodium chloride in water was added to the reaction mixture in equal-volume to the initial reaction volume. The resulting mixture was extracted three times with ethyl acetate, the organic layers collected, volatiles removed in vacuo and purified by silica gel column chromatography to provide (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-(3-chlorophenyl)pyrimidine-5-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Compound 8***). (MS (*m/z*) 592.0 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.39 (s, 2H), 8.98 (s, 1H), 8.63 – 8.40 (m, 2H), 8.28 (dd, *J* = 8.6, 2.6 Hz, 1H), 8.21 – 7.64 (m, 3H), 7.64 – 7.47 (m, 2H), 5.97 (d, *J* = 7.0 Hz, 1H), 4.01 (s, 3H), 1.63 (s, 3H).

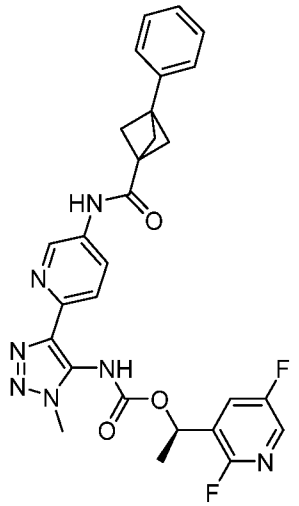
Example 9: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(1-(aminomethyl)-3,3-difluorocyclobutane-1-carboxamido)-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 9)



Compound 9

[0151] The title example was prepared from (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-amino-6-methylpyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 15***, 59 µmol) analogously to (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(2-cyclopropyloxazole-5-carboxamido)-6-methylpyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 7, step 3***) by replacing 2-cyclopropyloxazole-5-carboxylic acid with 1-[(*tert*-butoxycarbonylamino) methyl]-3,3-difluoro-cyclobutanecarboxylic acid (88 µmol, 1.5 eq). The resulting intermediate (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(1-(((*tert*-butoxycarbonyl)amino)methyl)-3,3-difluorocyclobutane-1-carboxamido)-6-methylpyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Intermediate 17***) was subjected to deprotection with trifluoroacetic acid in dichloromethane before concentration and flash chromatography (silica gel). (MS (*m/z*) 537.0 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 (m, 4H), 5.97 (s, 1H), 4.01 (s, 3H), 3.39 (s, 2H), 3.21 (dt, J = 15.7, 13.1 Hz, 2H), 2.92 – 2.71 (m, 2H), 2.48 (s, 3H), 1.62 (s, 3H).

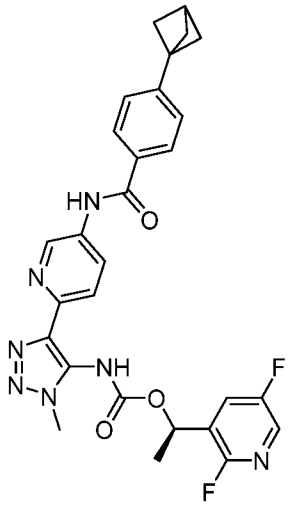
Example 10: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (1-methyl-4-(5-(3-phenylbicyclo[1.1.1]pentane-1-carboxamido)pyridin-2-yl)-1H-1,2,3-triazol-5-yl)carbamate (Compound 10)



Compound 10

[0152] The title example was prepared from (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 13***, 61 μmol) analogously to (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(6-cyclopropyl nicotinamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 6, step 3***) by replacing 6-cyclopropylpyridine-3-carboxylic acid with 3-phenylbicyclo[1.1.1]pentane-1-carboxylic acid (91 μmol, 1.5 eq). (MS (*m/z*) 546.1 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.89 (s, 1H), 8.30 – 7.60 (m, 4H), 7.41 – 7.20 (m, 5H), 5.95 (d, J = 7.7 Hz, 1H), 4.00 (s, 3H), 2.43 (s, 6H), 1.62 (s, 3H).

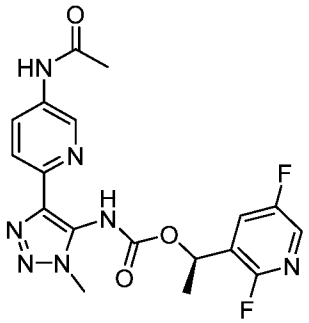
Example 11: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(4-(bicyclo[1.1.1]pentan-1-yl)benzamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 11)



Compound 11

[0153] The title example was prepared from (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 13***, 61 μmol) analogously to (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(6-cyclopropyl nicotinamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 6, step 3***) by replacing 6-cyclopropylpyridine-3-carboxylic acid with 4-(1-bicyclo[1.1.1]pentanyl)benzoic acid (91 μmol, 1.5 eq). (MS (*m/z*) 546.1 $[M+H]^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.96 (s, 1H), 8.23 (dd, *J* = 8.6, 2.6 Hz, 1H), 8.18 – 7.63 (m, 5H), 7.49 – 7.30 (m, 2H), 5.96 (d, *J* = 6.7 Hz, 1H), 4.00 (s, 3H), 2.60 (s, 1H), 2.17 (s, 6H), 1.62 (s, 3H).

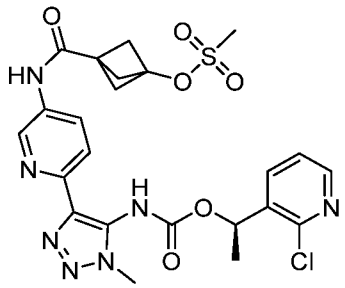
Example 12: (R)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-acetamidopyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate (Compound 12)



Compound 12

[0154] The title example was prepared from (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 13***, 1.1 mmol) analogously to (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-(6-cyclopropyl nicotinamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 6, step 3***) by replacing 6-cyclopropylpyridine-3-carboxylic acid with acetic acid (1.3 mmol, 1.2 eq). After concentration, instead of silica gel purification, the residue was subjected to reverse-phase HPLC to provide (*R*)-1-(2,5-difluoropyridin-3-yl)ethyl (4-(5-acetamidopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 12***). (MS (*m/z*) 418.1 $[M+H]^+$). ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.79 (bs, 1H), 8.68 (s, 1H), 8.20 (s, 1H), 8.07 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.98 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 5.79 (s, 1H), 3.88 (s, 3H), 2.10 (s, 3H), 1.56 (s, 3H).

Example 13: (R)-3-((6-(5-(((1-(2-chloropyridin-3-yl)ethoxy)carbonyl)amino)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)carbamoyl)bicyclo[1.1.1]pentan-1-yl methanesulfonate (Compound 13)



Compound 13

Step 1: (R)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(3-hydroxybicyclo[1.1.1]pentane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate dihydrochloride (Intermediate 18)

[0155] The title intermediate was prepared from (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-aminopyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate hydrochloride (***Intermediate 7***, 0.11 mmol) analogously to (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(1-hydroxycyclopropane-1-carboxamido)pyridin-2-yl)-1-methyl-1*H*-1,2,3-triazol-5-yl)carbamate (***Example 3, step 3***) by replacing 1-hydroxycyclopropanecarboxylic acid with 3-hydroxybicyclo[1.1.1]pentane-1-carboxylic acid (0.13 mmol). After concentration of the reaction mixture, the residue was subjected to reverse-phase HPLC. The residue was co-evaporated from a solution of hydrogen chloride in dioxane (4M, 10 mL) to provide, after concentration under reduced pressure, (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(3-hydroxybicyclo[1.1.1]pentane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate dihydrochloride (***Intermediate 18***). (MS (*m/z*) 484.1 $[M+H]^+$).

Step 2: (R)-3-((6-(5-(((1-(2-chloropyridin-3-yl)ethoxy)carbonyl)amino)-1-methyl-1H-1,2,3-triazol-4-yl)pyridin-3-yl)carbamoyl)bicyclo[1.1.1]pentan-1-yl methanesulfonate (Compound 13)

[0156] A solution of (*R*)-1-(2-chloropyridin-3-yl)ethyl (4-(5-(3-hydroxybicyclo[1.1.1]pentane-1-carboxamido)pyridin-2-yl)-1-methyl-1H-1,2,3-triazol-5-yl)carbamate

dihydrochloride (***Intermediate 18***, 68 μmol) in dichloromethane (2 mL) was treated with triethylamine (0.34 mmol) at room temperature. To the stirred mixture was added methanesulfonyl chloride (0.40 mmol). When LC/MS analysis deemed the reaction completed, the mixture was quenched with isopropanol and concentrated under reduced pressure. The residue was subjected to reverse-phase HPLC to provide (*R*)-3-((6-(5-(((1-(2-chloropyridin-3-yl)ethoxy)carbonyl)amino)-1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-3-yl)carbamoyl)bicyclo[1.1.1]pentan-1-yl methanesulfonate (***Compound 13***). (MS (*m/z*) 562.1 $[M+H]^+$). ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.91 (s, 1H), 8.55 (s, 1H), 8.31 (d, *J* = 3.2 Hz, 1H), 8.15 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.90 (bs, 1H), 7.38 (bs, 1H), 6.01 (q, *J* = 6.5 Hz, 1H), 3.93 (s, 3H), 3.10 (s, 3H), 2.59 (s, 6H), 1.55 (s, 3H).

Example 14: Calcium Assay

[0157] *In vitro* LPAR1 activity was measured in an intracellular calcium mobilization assay.

[0158] CHO-K1 EDG2 cells (DiscoverX cat# 93-0644C2) expressing human LPAR1 (NM_001401.3) were seeded in a total volume of 25 μL of Dulbecco's Modification of Eagle's Medium (DMEM) with 10% Fetal Bovine Serum, 1x PenStrepGlutamine, 300μg/ml Hygromycin, and 800μg/ml G418 into 384-well tissue culture plate (Grenier # 781091) at 15,000 cells/well and incubated at 37°C overnight. Prior to testing, 25 μL Calcium Loading Dye Component A (FLIPR Calcium 6 Assay Kit Molecular Device # R8190) and 2.5 mM Probenecid (Invitrogen # P36400, prepared fresh) in Hank's Balanced Salt Solution (Corning # 21-023-CV), 20 mM HEPES (Corning # 25-060-CI), 0.1% Bovine Serum Albumin (Sigma-Aldrich # A7906-500G) was add to the cells for 60 minutes at 37°C.

[0159] Agonist dose curves of LPA 18:2 (Avanti Polar Lipids cat# 857138, 0.5nM to 10 μM) were recorded to determine the LPA 18:2 EC_{80} for subsequent antagonist assays. For agonist dose curves, cells were removed from the incubator 2 hours after dye loading and transferred to the FLIPR Tetra instrument (Molecular Devices, San Jose, CA). Calcium mobilization was monitored for 5 min and 10 μL 6X LPA in HBSS / 20 mM Hepes / 0.1% bovine serum albumin (BSA) was added to the cells 5 seconds into the assay.

[0160] To determine the LPAR1 antagonist activity of test compounds, cells were pre-incubated with test compound at a dose range of 0.5 nM to 10 μM, followed by LPA at EC_{80} concentration

(100 nM). After dye loading, cells were removed from the incubator and 0.3 µL of 200X antagonist was added. Cells were incubated for 60 minutes at 37°C. Antagonist activity was measured on a FLIPR Tetra. Calcium mobilization was monitored for 3.5 minutes and 10 µL 6X EC_{80} LPA in HBSS, 20 mM HEPES, and 0.1% BSA was added to the cells 5 seconds into the assay. Signal amplitude (Maximum minus minimum) values were plotted against log_{10} of antagonist concentration using Dose Response Tool (Gilead Sciences Inc.) to determine EC_{50}.

[0161] To assess the antagonistic potential of exemplified compounds EC_{50} values were determined for Compounds 1 to 13 in the LPAR1 calcium mobilization assay. Results are shown in Table 1 (LPAR1 EC_{50}). The compound numbers correspond to the compound numbers in Examples 1 to13.

Table 1

Compound	**LPAR1** (EC_{50}; nM)
Compound 1	345
Compound 2	36,956
Compound 3	2,771
Compound 4	1,255
Compound 5	186
Compound 6	176
Compound 7	261
Compound 8	22
Compound 9	34
Compound 10	13
Compound 11	365
Compound 12	2,052
Compound 13	152

* * *

[0162] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

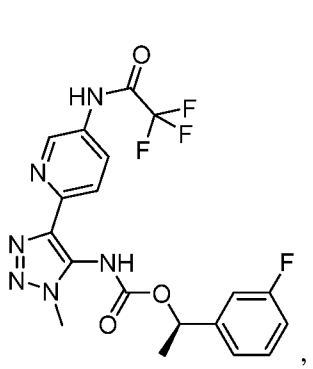
[0163] Thus, it should be understood that although the present disclosure has been specifically disclosed by preferred embodiments and optional features, modification, improvement and variation of the disclosures embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this disclosure. The materials, methods, and examples provided here are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the disclosure.

[0164] The disclosure has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the disclosure with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0165] It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

CLAIMS

1. A compound selected from the group consisting of: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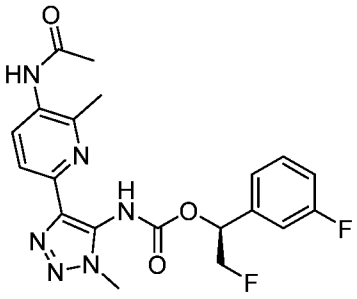
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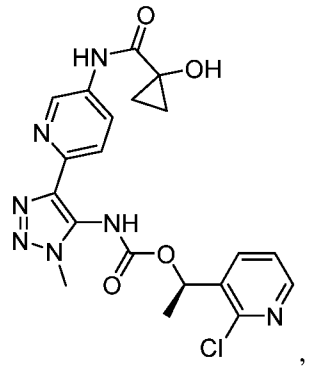
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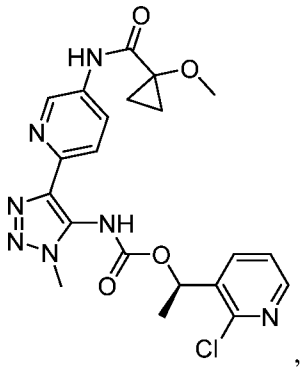
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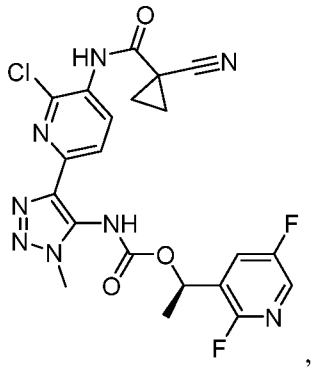
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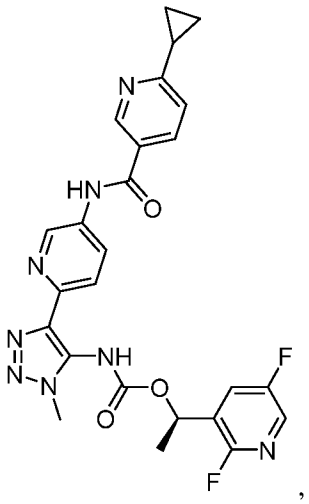
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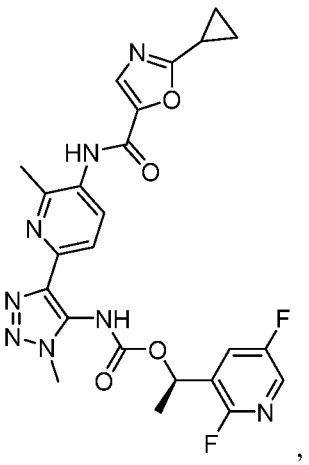
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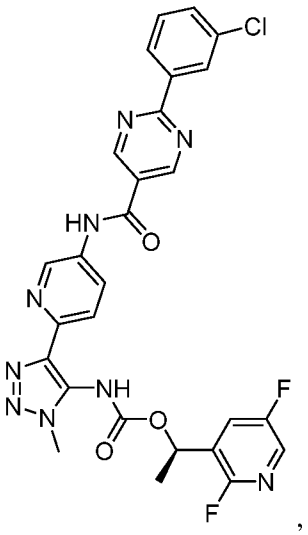
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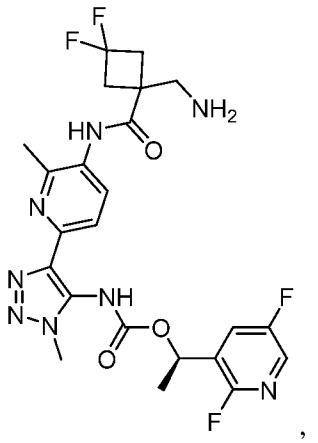
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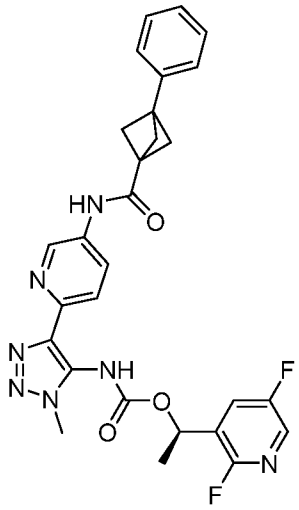
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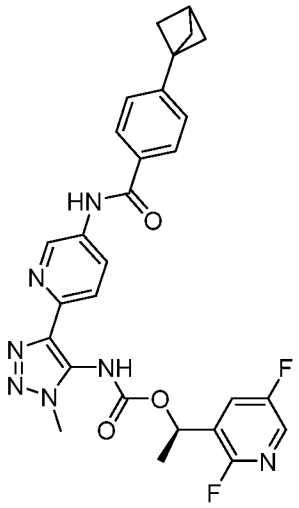
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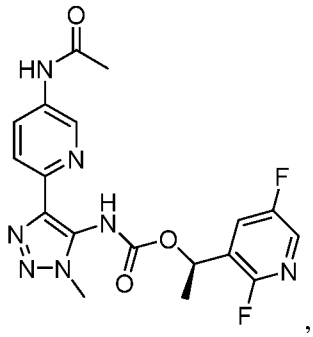
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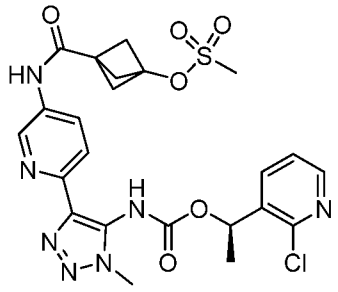
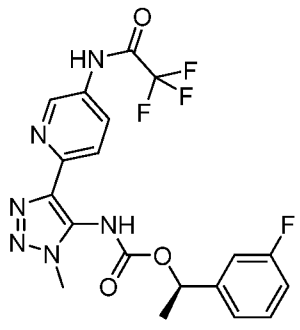

and , or a pharmaceutically acceptable salt thereof.

2. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is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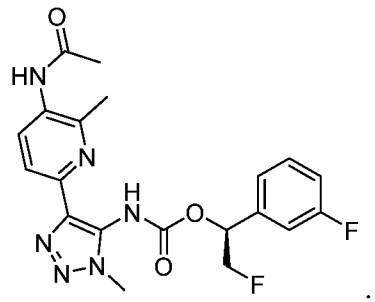
3. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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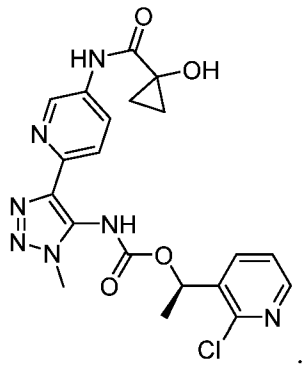
4. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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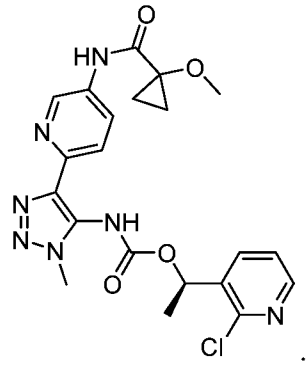
5. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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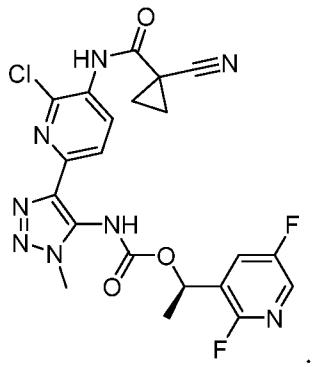
6. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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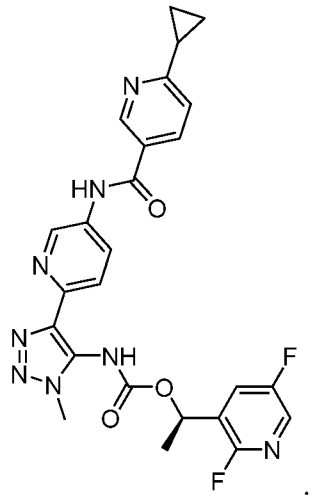
7. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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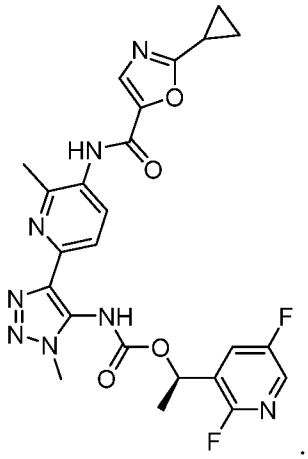
8. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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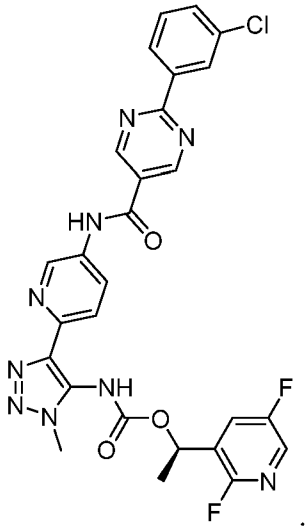
9. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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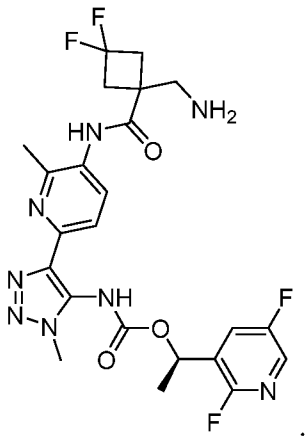
10. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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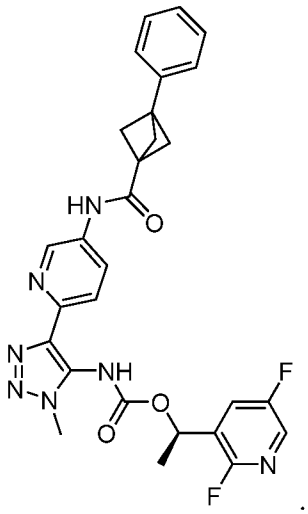
11. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



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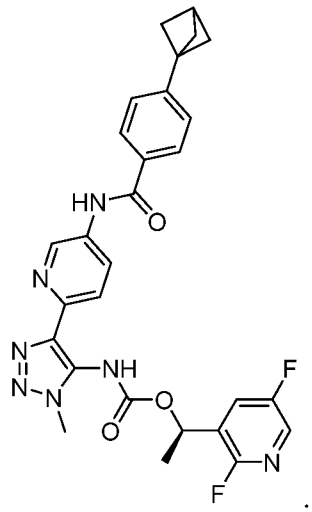
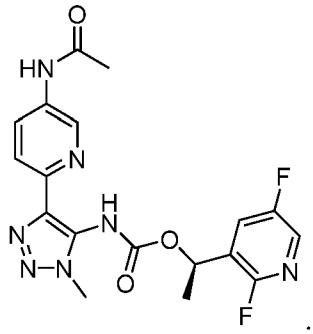
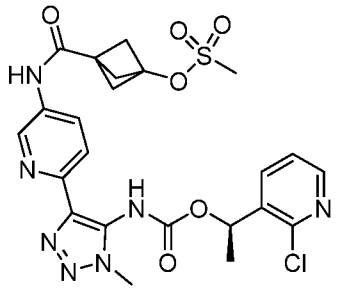
12. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



13. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



14. A compound or pharmaceutically acceptable salt thereof of claim 1, wherein the compound is



15. A pharmaceutical composition comprising a therapeutically effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 14, and a pharmaceutically acceptable excipient.

16. The pharmaceutical composition of claim 15, further comprising an additional therapeutic agent.

17. A method of treating, stabilizing, or lessening the severity or progression of an LPAR1 mediated disease or condition comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claims 15 or 16.

18. The method of claim 17, wherein the LPAR1 mediated disease or condition is selected from the group consisting of wound healing, cancer, pain, respiratory disorder, allergic disorder, nervous system disorder, cardiovascular disorder, and inflammatory disorder.

19. The method of claim 17, wherein the LPAR1 mediated disease or condition is an interstitial lung disease (ILD).

20. The method of claim 19, wherein the interstitial lung disease (ILD) is nonspecific interstitial pneumonitis (NSIP), sarcoidosis, asbestosis, an ILD related to an occupational exposure, progressive fibrosing ILD, idiopathic interstitial pneumonia (IIP), connective tissue disease-associated interstitial lung disease (CTD-ILD), rheumatoid arthritis-associated ILD, scleroderma-associated ILD, or extrinsic alveolar alveolitis.

21. The method of claim 17, wherein the LPAR1 mediated disease or condition is a chronic kidney disease (CKD).

22. The method of claim 21, wherein the CKD is complement glomerulopathy, membranous glomerulopathy, polycystic kidney disease, IgA nephropathy, focal segmental glomerulosclerosis (FSGS), or Alport Syndrome.

23. The method of claim 17 or 18, wherein the LPAR1 mediated disease or condition comprises fibrosis.

24. The method of claim 23, wherein fibrosis is pulmonary fibrosis, renal fibrosis, hepatic fibrosis, ocular fibrosis, cardiac fibrosis, or systemic sclerosis.

25. The method of claim 24, wherein pulmonary fibrosis is idiopathic pulmonary fibrosis (IPF) or Progressive Fibrotic interstitial lung disease (PF-ILD).

26. The method of claim 24, wherein the pulmonary fibrosis is secondary to a systemic inflammatory disease.

27. The method of claim 26, wherein the systemic inflammatory disease is 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 or acute respiratory distress.

28. The method of claim 24, wherein the renal fibrosis is associated with diabetic kidney disease.

29. The method of claim 17, wherein the LPAR1 mediated disease or condition is a liver disease.

30. The method of claim 29, wherein the liver disease comprises liver fibrosis.

31. The method of claim 29 or 30, wherein the liver disease comprises non-alcoholic fatty liver disease (NAFLD).

32. The method of any one of claims 29-31, wherein the liver disease comprises steatosis.

33. The method of any one of claims 29-32, wherein the liver disease comprises non-alcoholic steatoheptitis (NASH).

34. The method of any one of claims 29-33, wherein the liver disease comprises liver cirrhosis.

35. The method of claim 34, wherein the liver cirrhosis is compensated liver cirrhosis.

36. The method of claim 34, wherein the liver cirrhosis is decompensated liver cirrhosis.

37. The method of any one of claims 29-36, wherein the liver disease comprises hepatocellular carcinoma (HCC).

38. The method of any one of claims 29-37, wherein the liver disease comprises Primary Biliary Cirrhosis (PBC) or Primary Sclerosing Choleangitis (PSC).

39. The method of any one of claims 29-38, wherein the liver disease comprises portal hypertension.

40. The method of any one of claims 17-39, wherein the compound or pharmaceutically acceptable salt thereof is administered in combination with an additional therapeutic agent.

41. The pharmaceutical composition of claim 16 or the method of claim 40, wherein the additional therapeutic agent is one, two, three, or four additional therapeutic agents.

42. The pharmaceutical composition of claim 16, or the method of claim 40 or 41, wherein the additional therapeutic agent comprises an acetyl-CoA carboxylase (ACC) inhibitor, an apoptotic signal-regulating kinase (ASK-1) inhibitor, a farnesoid X receptor (FXR) agonist, fish oil, a glucagon-like peptide-1 receptor agonist, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, or a TGFβ antagonist.

43. The pharmaceutical composition or method of claim 42, wherein the the ACC inhibitor is firsocostat.

44. The pharmaceutical composition or method of claim 42, wherein the the ASK1 inhibitor is selonsertib.

45. The pharmaceutical composition or method of claims 42, wherein the the FXR agonist is cilofexor.

46. The pharmaceutical composition or method of claim 42, wherein the PPARα agonist is a fibrate.

47. The pharmaceutical composition or method of claim 42, wherein the fish oil is icosapent ethyl.

48. The pharmaceutical composition or method of claim 42, wherein the GLP-1 receptor agonist is liraglutide or semaglutide.

49. The pharmaceutical composition or method of claim 42, wherein the TGFβ antagonist is an anti-TGFβ1 specific antibody.

50. The pharmaceutical composition or method of claim 42, wherein the TGFβ antagonist is a TGFβ receptor.

51. The pharmaceutical composition or method of claim 42, wherein the additional therapeutic agents comprise firsocostat and cilofexor.

52. The pharmaceutical composition or method of claim 42, wherein the additional therapeutic agents comprise firsocostat, and liraglutide or semaglutide.

53. The pharmaceutical composition or method of any one of claims 43, 51, or 52, wherein the additional therapeutic agents comprise a fibrate or icosapent ethyl.

54. The pharmaceutical composition or method of claim 41, wherein the additional therapeutic agents comprise cilofexor and liraglutide or semaglutide.

55. The pharmaceutical composition of claim 16, or the method of claim 40 or 41, wherein the additional therapeutic agent comprises a VEGFR inhibitor, a FGFR inhibitor, a PDGFR inhibitor, an autaxin inhibitor, a GPR84 agonist, a PASK inhibitor, a CFTR agonist, a JAK1 inhibitor, an ADAMTS5 inhibitor, a TOL2/3 inhibitor, a CTGF inhibitor, a soluble PTX2, an anti-galectin-3 antibody, an integrin-α_V-β_6/α_V-β_1 antagonist, a JNK1 inhibitor, a mineralocorticoid receptor antagonist, a Nrf2 activator, a chymase inhibitor, a PDE inhibitor, a NOX1/4 inhibitor, a leukotriene/thromboxane receptor antagonist, SLC22A12 inhibitor, an sGC inhibitor, or a xanthine oxidase inhibitor.

56. The pharmaceutical composition of claim 16, or the method of claim 40 or 41, wherein the additional therapeutic agent is selected from the group consisting of nintedanib, pirfenidone, pamrevlumab, PRM-151, GB-0139, PLN-74809, CC-90001, finerenone, BAY1142524, PCS-499, setanaxib, SER150, RDEA3170, praliciguat, TMX-049,

GLPG1690, GLPG1205, GLPG1972, GLPG4059, GLPG2737, GLPG3970, and filgotinib.

57. Use of a compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 16 for the manufacture of a medicament for the treatment of an LPAR1 mediated disease or condition.