TREATMENT OF PULMONARY OR RESPIRATORY DISEASES BY INHALATION ADMINISTRATION OF PI3 KINASE INHIBITORS

Effect of Compound 1 on LPS-induced Neutrophilia in BAL (4 hours duration)

Abstract: Provided herein are methods of treating, preventing and/or managing a pulmonary or respiratory disease by administering by inhalation to a subject the compound of formula (I) or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound. Formulations for administration by inhalation and kits comprising the same are also provided.
Published:

— with international search report (Art. 21(3))
TREATMENT OF PULMONARY OR RESPIRATORY DISEASES BY INHALATION ADMINISTRATION OF PI3 KINASE INHIBITORS

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/000,911, filed May 20, 2014, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] Asthma is a chronic inflammatory disease of the airways that affects people of all ages. An estimated 300 million people have the disease worldwide, with the prevalence varying by country globally from 1 to 18%. The World Health Organization (WHO) has estimated that asthma is associated with an annual loss of 15 million disability-adjusted life years (DALY), accounting for approximately 1% of the total healthcare burden. Worldwide as many as 250,000 patients die from asthma each year. It is estimated that 5 to 10% of asthma patients have severe and/or refractory asthma that is not well managed with current therapies. See Wenzel S., American Journal of Respiratory and Critical Care Medicine, 2005, 172(2): 149-60.

[0003] Treatment of severe and/or refractory asthma remains highly problematic, with systemic corticosteroids often used to control symptoms. Id. See also, Holgate ST, Polosa R., Lancet., 2006, 368(9537):780-93. Long-term use of systemic corticosteroids is associated with well-known side effects, including hyperglycemia, increased susceptibility to infections, myopathy, cataracts, and osteoporosis. Resistance or poor responsiveness to corticosteroids is characteristic of many severe/refractory asthmatics, thus control may not be achieved despite long-term use of potentially toxic medication. At this time there remains an unmet clinical need for novel agents for severe/refractory asthma.

[0004] PI3K δ and γ have been shown in preclinical studies to modulate inflammatory pathways and cell types believed to be important in asthma and allergic inflammation. Importantly, many of the pathways affected by PI3K δ/γ inhibition are different from those affected by corticosteroids, thus a PI3K inhibitor represents a potentially novel anti-inflammatory agent with the ability to impact asthmatic inflammation in ways that are different from currently available therapies.

SUMMARY

[0005] Methods, compositions, and kits for treating or preventing a pulmonary or respiratory disease in a subject are provided herein. The methods, compositions and kits include administering a PI3K inhibitor, alone or in combination with other agents or therapeutic modalities, to a subject (e.g., a mammalian subject, e.g., a human) in need thereof by inhalation a therapeutically or prophylactically effective amount of a PI3K inhibitor. Disclosed herein is, at least in part, that a PI3 kinase (PI3K) inhibitor, as a single agent or in combination with one or more additional therapies, can ameliorate a pulmonary or respiratory disease (e.g., by decreasing one or more symptoms associated with the pulmonary or respiratory disease) in a subject, e.g., a mammalian subject, e.g., a human.
Also provided herein are methods, compositions, and kits for eliciting prolonged anti-inflammatory effect in lung in a subject suffering from a pulmonary or respiratory disease, comprising administering to the subject by inhalation a therapeutically or prophylactically effective amount of a PI3K inhibitor. In one embodiment, the PI3K inhibitor is retained in lung for a period longer than what is provided by oral administration.

In another embodiment, the PI3K inhibitor is delivered locally to the site of inflammation, e.g., via inhalation.

In one embodiment, provided herein is a method of treating, preventing, and/or managing a pulmonary or respiratory disease in a subject, comprising administering to a subject in need thereof by inhalation a therapeutically or prophylactically effective amount of a PI3K inhibitor, wherein the PI3K inhibitor is a compound of formula (I):

![Chemical Structure](image)

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound.

In one embodiment, provided herein is a method of eliciting prolonged anti-inflammatory effect in lung in a subject suffering from a pulmonary or respiratory disease, comprising administering to the subject by inhalation a therapeutically or prophylactically effective amount of a PI3K inhibitor, wherein the PI3K inhibitor is retained in lung for a period longer than what is provided by oral administration, and wherein the PI3K inhibitor is a compound of formula (I):

![Chemical Structure](image)

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound.

**INCORPORATION BY REFERENCE**

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference in their entirety and to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.
BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1A depicts the effect of Compound 1 (normalized) on LPS induced neutrophilia in bronchoalveolar lavage fluid (BALF) following administration by inhalation.

[0011] FIG. 1B depicts the effect of Compound 1 (raw data) on LPS induced neutrophilia in BALF following administration by inhalation.

[0012] FIG. 2A shows that Compound 1 is active in rat ovalbumin-induced asthma model as measured by white blood cells.

[0013] FIG. 2B shows that Compound 1 is active in rat ovalbumin-induced asthma model as measured by eosinophils.

DETAILED DESCRIPTION

DEFINITIONS

[0014] While preferred embodiments of the present invention have been shown and described herein, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein can be employed in practicing the invention. It is intended that the appended claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[0015] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

[0016] As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

[0017] As used herein, the term "patient" or "subject" refers to an animal, typically a human (i.e., a male or female of any age group, e.g., a pediatric patient (e.g., infant, child, adolescent) or adult patient (e.g., young adult, middle-aged adult or senior adult) or other mammal, such as a primate (e.g., cynomolgus monkey, rhesus monkey); other mammals such as rodents (mice, rats), cattle, pigs, horses, sheep, goats, cats, dogs; and/or birds, that will be or has been the object of treatment, observation, and/or experiment. When the term is used in conjunction with administration of a compound or drug, then the patient has been the object of treatment, observation, and/or administration of the compound or drug.

[0018] "Treating," "treat," and "treatment" as used herein, refers to partially or completely inhibiting or reducing the condition from which the subject is suffering. In one embodiment, this term refers to an action that occurs while a patient is suffering from, or is diagnosed with, the condition, which reduces the severity of the condition, or retards or slows the progression of the condition. Treatment need not result in a complete cure of the condition; partial inhibition or reduction of the condition is encompassed by this term.
"Therapeutically effective amount," as used herein, refers to a minimal amount or concentration of a PI3K inhibitor that, when administered alone or in combination, is sufficient to provide a therapeutic benefit in the treatment of the condition, or to delay or minimize one or more symptoms associated with the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent. The therapeutic amount need not result in a complete cure of the condition; partial inhibition or reduction of the condition is encompassed by this term. The therapeutically effective amount can also encompass a prophylactically effective amount.

As used herein, unless otherwise specified, the terms "prevent," "preventing" and "prevention" refers to an action that occurs before the subject begins to suffer from the condition, or relapse of the condition. The prevention need not result in a complete prevention of the condition; partial prevention or reduction of the condition or a symptom of the condition, or reduction of the risk of developing the condition, is encompassed by this term.

As used herein, unless otherwise specified, a "prophylactically effective amount" of a PI3K inhibitor that, when administered alone or in combination, prevents or reduces the risk of developing the condition, or one or more symptoms associated with the condition, or prevents its recurrence. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent. The prophylactic amount need not result in a complete prevention of the condition; partial prevention or reduction of the condition is encompassed by this term.

As used herein, to "decrease", "ameliorate," "reduce," "treat" (or the like) a condition or symptoms associated with the condition includes reducing the severity and/or frequency of symptoms of the condition, as well as preventing the condition and/or symptoms of the condition (e.g., by reducing the severity and/or frequency of flares of symptoms). In some embodiments, the symptom is reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the pre-treatment level in the sample or subject treated, or it can be the level in a control population (e.g., the level in subjects who do not have the condition or the level in samples derived from subjects who do not have the condition). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

As used herein, "agent" or "biologically active agent" refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include simple or complex organic or inorganic molecule, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, antibody fragment, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound. Various compounds can be synthesized, for example, small molecules and oligomers (e.g., oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant
or animal extracts, and the like. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of the present invention.

[0024] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function of a target protein (e.g., a PI3K, e.g., PBK -δ), whether by inhibiting the activity or expression of the target protein. Accordingly, the terms "antagonist" and "inhibitors" are defined in the context of the biological role of the target protein. While antagonists can specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition.

[0025] As used herein, a "phosphoinositide 3-kinase (PI3K) inhibitor" or "PI3K inhibitor" refers to an inhibitor of any PI3K. PBKs are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositol or phosphoinositides. The PI3K family includes kinases with distinct substrate specificities, expression patterns, and modes of regulation (see, e.g., Katso et al., 2001, Annu. Rev. Cell Dev. Biol. 17, 615-675; Foster, F.M. et al, 2003, J Cell Sci 116, 3037-3040). The class I PBKs (e.g., p10 a, p10 β, p10 γ, and p10 δ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream mediators such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II PBKs (e.g., PI3K-C2a, PI3K-C2P, PBK-C2y) and III PBKs (e.g., Vps34) play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. Specific exemplary PBK inhibitors are disclosed herein.

[0026] The class I PBKs comprise a p10 catalytic subunit and a regulatory adapter subunit. See, e.g., Cantrell, D.A. (2001) Journal of Cell Science 114: 1439-1445. Four isoforms of the p10 subunit (including PBK-a (alpha), PBK -β (beta), PBK -γ (gamma), and PBK -δ (delta) isoforms) have been implicated in various biological functions. Class I PBKα is involved, for example, in insulin signaling, and has been found to be mutated in solid tumors. Class I PBK -β is involved, for example, in platelet activation and insulin signaling. Class I PBK -γ plays a role in mast cell activation, innate immune function, and immune cell trafficking (chemokines). Class I PBK -δ is involved, for example, in B-cell and T-cell activation and function and in Fc receptor signaling in mast cells. In some embodiments provided herein, the PBK inhibitor is a class I PBK inhibitor. In some such embodiments, the PBK inhibitor inhibits a PBK-a (alpha), PBK -β (beta), PBK -γ (gamma), or PBK -δ (delta) isoform, or a combination thereof.

[0027] Downstream mediators of PBK signal transduction include Akt and mammalian target of rapamycin (mTOR). Signal transduction such as Akt that possesses a pleckstrin homology (PH) domain can bind to PIP3, leading to the activation of downstream signaling including Akt activation. Akt phosphorylates many substrates and is a central downstream effector of PBK for diverse cellular responses. One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PBK family.
The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutical acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

"Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The term "selective inhibition" or "selectively inhibit" as applied to a biologically active agent refers to the agent's ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or interact interaction with the target. For example, a compound that selectively inhibits one isoform of PI3K over another isoform of PI3K has an activity of at least greater than about 1X against a first isoform relative to the compound's activity against the second isoform (e.g., at least about 2X, 3X, 5X, 10X, 20X, 50X, 100X, 200X, 500X, or 1000X).

"Radiation therapy" means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as alpha-particle emitting radionucleotides (e.g., actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (i.e., beta emitters), conversion electron emitters (e.g., strontium-89 and samarium-153-EDTMP, or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons.

"Prodrug" is meant to indicate a compound that can be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug can be inactive when administered to
a subject, but is converted in vivo to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, Chapter 1, pages 1-12, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, can be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like.

The term "in vivo" refers to an event that takes place in a subject's body.

The term "in vitro" refers to an event that takes places outside of a subject's body. For example, an in vitro assay encompasses any assay run outside of a subject assay. In vitro assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures wherein hydrogen is replaced by deuterium or tritium, or wherein carbon atom is replaced by 13C- or 14C-enriched carbon, are within the scope of this invention.

The compounds described herein can also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds can be radiolabeled with radioactive isotopes, such as for example tritium (3H), iodine-125 (125I) or carbon-14 (14C). All isotopic variations of the compounds described herein, whether radioactive or not, are encompassed within the scope of the present invention.

When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range can vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or
"having" or "including") includes those embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, that "consist of" or "consist essentially of" the described features.

[0038] The following abbreviations and terms have the indicated meanings throughout: PI3-K = Phosphoinositide 3-kinase; PI = phosphatidylinositol; PDK = Phosphoinositide Dependent Kinase; DNA-PK = Deoxyribose Nucleic Acid Dependent Protein Kinase; PTEN = Phosphatase and Tensin homolog deleted on chromosome Ten; PIKK = Phosphoinositide Kinase Like Kinase; AIDS = Acquired Immuno Deficiency Syndrome; HIV = Human Immunodeficiency Virus; Mel = Methyl Iodide; POCl3 = Phosphorous Oxychloride; KCNS = Potassium IsoThiocyanate; TLC = Thin Layer Chromatography; MeOH = Methanol; and CHC13 = Chloroform.

[0039] Abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0040] "Isomers" are different compounds that have the same molecular formula. "Steroisomers" are isomers that differ only in the way the atoms are arranged in space, i.e., having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0041] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which can potentially have an (R)- or an (S)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (R)- or (S)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (S)- and 20% (R)-, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or the Pirkle alcohol, or derivatization of a compounds.
using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[0042] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[0043] The compounds of the present invention can also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds can be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0044] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., OCH₂⁻ is equivalent to CH₂O⁻.

[0045] Compounds that can be used as described herein also include crystalline and amorphous forms of compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0046] As used herein, and unless otherwise specified, "polymorph" can be used herein to describe a crystalline material, e.g., a crystalline form. In certain embodiments, "polymorph" as used herein are also meant to include all crystalline and amorphous forms of a compound or a salt thereof, including, for example, crystalline forms, polymorphs, pseudopolymorphs, solvates, hydrates, co-crystals, unsolvated polymorphs (including anhydrates), conformational polymorphs, tautomeric forms, disordered crystalline forms, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds of the present disclosure include crystalline and amorphous forms of those compounds, including, for example, crystalline forms, polymorphs, pseudopolymorphs, solvates, hydrates, co-crystals, unsolvated polymorphs (including anhydrates), conformational polymorphs, tautomeric forms, disordered crystalline forms, and amorphous forms of the compounds or a salt thereof, as well as mixtures thereof.

[0047] Chemical entities include, but are not limited to, compounds of Formula (I), and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include...
pharmaceutically acceptable salts, chelates, non-covalent complexes, prodrugs, and mixtures thereof. In certain embodiments, the compounds described herein are in the form of pharmaceutically acceptable salts. Hence, the terms "chemical entity" and "chemical entities" also encompass pharmaceutically acceptable salts, chelates, non-covalent complexes, prodrugs, and mixtures.

[0048] In addition, if the compound of Formula I is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, can be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that can be used to prepare non-toxic pharmaceutically acceptable addition salts.

COMPOUNDS

[0049] The compounds provided below are exemplary PI3K inhibitors that can be used in the pharmaceutical compositions, methods and kits disclosed herein.

[0050] In some embodiments, the PI3K inhibitor is a compound of formula (I) (also referred as Compound 1 herein):

![Chemical Structure]

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

[0051] Compound 1 has a chemical name of (S)-2-amino-4-(((1-(8-(2-methoxypyridin-4-yl)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)amino)pyrimidine-5-carbonitrile. Compound 1 also refers to any crystal form or polymorph of (S)-2-amino-4-(((1-(8-(2-methoxypyridin-4-yl)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)amino)pyrimidine-5-carbonitrile. An exemplary method for synthesizing Compound 1 has been previously described in U.S. Patent Application Publication No. 2013/0053362, which is incorporated by reference in its entirety.

[0052] The compound of formula (I) provided herein contains one chiral center, and can exist as a mixture of enantiomers, e.g., a racemic mixture. This disclosure encompasses the use of stereomerically pure forms of such a compound, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of the compound of formula (I) provided herein can be used in methods and compositions disclosed herein. These isomers can be asymmetrically synthesized or resolved using standard

[0053] In one embodiment, the PI3K inhibitor provided herein is a mixture of Compound 1 and its (R)-enantiomer. In one embodiment, the PI3K inhibitor provided herein is a racemic mixture of Compound 1 and its (R)-enantiomer. In other embodiments, the compound mixture has an (S)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In other embodiments, the compound mixture has an (S)-enantiomeric purity of greater than about 55% to about 65%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[0054] In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[0055] In some embodiments, a polymorph of a compound, or a salt, solvate (e.g., hydrate), or solvate of a salt thereof, disclosed herein is used. Exemplary polymorphs are disclosed in International Patent Application No. PCT/US 14/25622 (published as WO2014/151386), which is hereby incorporated by reference in their entireties. In one embodiment, the compound is Form 1 of a sulfuric acid salt of Compound 1. In one embodiment, the compound is Form 1A of a sulfuric acid salt of Compound 1. In one embodiment, the compound is Form 1B of a sulfuric acid salt of Compound 1. In one embodiment, the compound is Form 2 of a sulfuric acid salt of Compound 1. In one embodiment, the compound is Form 3 of a sulfuric acid salt of Compound 1. In one embodiment, the compound is Form 1 of a maleic acid salt of Compound 1. In one embodiment, the compound is Form 1 of a 1,2-ethanedisulfonic acid salt of Compound 1. In one embodiment, the compound is Form 2 of a 1,2-ethanedisulfonic acid salt of Compound 1. In one embodiment, the compound is Form 3 of a 1,2-ethanedisulfonic acid salt of Compound 1. In one embodiment, the compound is Form 4 of a 1,2-ethanedisulfonic acid salt of Compound 1. In one embodiment, the compound is Form 1 of a hydrochloride salt of Compound 1.
isethionate salt of Compound 1. In one embodiment, the compound is Form 1 of a free base of Compound 1. In one embodiment, the compound is Form 2 of a free base of Compound 1. In one embodiment, the compound is Form 3 of a free base of Compound 1. In one embodiment, the compound is Form 4 of a free base of Compound 1. In one embodiment, the compound is Form 5 of a free base of Compound 1. In one embodiment, the compound is Form 6 of a free base of Compound 1. In one embodiment, the compound is a mixture of solid forms (e.g., polymorphs and/or amorphous forms) of Compound 1 disclosed herein.

[0056] Any of the compounds disclosed herein can be in the form of pharmaceutically acceptable salts, hydrates, solvates, chelates, non-covalent complexes, isomers, prodrugs, isotopically labeled derivatives, or mixtures thereof.

[0057] It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of the structure.

METHODS OF TREATMENT, PREVENTION AND/OR MANAGEMENT

[0058] Without being limited by a particular theory, it was found that administering a compound provided herein (e.g., Compound 1) by inhalation can accord various therapeutic benefits as described herein in treating, preventing and/or managing pulmonary or respiratory diseases. Accordingly, in certain embodiments, provided herein is a method of treating, preventing, and/or managing a pulmonary or respiratory disease in a subject, comprising administering to a subject in need thereof by inhalation a therapeutically or prophylactically effective amount of a compound provided herein, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound. In some embodiments, provided herein is a method of treating, preventing, and/or managing a pulmonary or respiratory disease in a subject, comprising administering to a subject in need thereof by inhalation a therapeutically or prophylactically effective amount of a PI3Kδ/γ dual inhibitor, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound. In certain embodiments, provided herein is a method of treating, preventing, and/or managing a pulmonary or respiratory disease in a subject, comprising administering to a subject in need thereof by intratracheal administration to the lungs a therapeutically or prophylactically effective amount of a compound provided herein, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound. In some embodiments, provided herein is a method of treating, preventing, and/or managing a pulmonary or respiratory disease in a subject, comprising administering to a subject in need thereof by intratracheal administration to the lungs a therapeutically or prophylactically effective amount of a PI3Kδ/γ dual inhibitor, or an enantiomer or a
mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound.

[0060] In addition, without being limited by a particular theory, it was found that administering a compound provided herein by inhalation results in a prolonged retention of the compound in a subject suffering from a pulmonary or respiratory disease, comprising administering to the subject by inhalation a therapeutically or prophylactically effective amount of a compound provided herein, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound, wherein the compound is retained in lung for a prolonged period (e.g., a period longer than what is provided by oral administration).

[0061] In some embodiments, the compound is retained in lung for about hour, about 3 hours, about 6 hours, about 12 hours, about 24 hours, about 48 hours, or about 72 hours longer than what is provided by oral administration.

[0062] In one embodiment, the compound is retained in lung for about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 12 hours, about 24 hours, about 48 hours, or about 72 hours. In one embodiment, the compound is retained in lung for about 1 hour. In another embodiment, the compound is retained in lung for about 3 hours.

[0063] In other embodiments, more than 80%, more than 70%, more than 60%, more than 50%, more than 40%, more than 30%, or more than 20% of the amount of the compound as initially administered to patient remains in lung at 24 hours after administration by inhalation.

[0064] In other embodiments, the concentration of the compound in lung following administration by inhalation is about 100, about 200, about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, or about 10000 times higher than the plasma concentration of the compound at about 5 hours after the administration. In other embodiments, the concentration of the compound in lung following administration by inhalation is about 100, about 200, about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, or about 10000 times higher than the plasma concentration of the compound at about 12 hours after the administration. In other embodiments, the concentration of the compound in lung following administration by inhalation is about 100, about 200, about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, or about 10000 times higher than the plasma concentration of the compound at about 24 hours after the administration.

[0065] In some embodiments, the amount of the compound inhaled by the subject is less than 0.01 µg/kg, less than 0.02 µg/kg, less than 0.05 µg/kg, less than 0.1 µg/kg, less than 0.2 µg/kg, less than 0.5 µg/kg, less than 1 µg/kg, less than 2 µg/kg, less than 5 µg/kg, less than 10 µg/kg, less than 20 µg/kg, less than 50 µg/kg, or less than 100 µg/kg. In other embodiments, the amount of the compound inhaled by the subject is about 0.01 µg/kg, about 0.02 µg/kg, about 0.05 µg/kg, about 0.1 µg/kg, about 0.2 µg/kg, about 0.5 µg/kg, about 1 µg/kg, about 2 µg/kg,
about 5 µg/kg, about 10 µg/kg, about 20 µg/kg, about 50 µg/kg, or about 100 µg/kg. In other embodiments, the amount of the compound inhaled by the subject is from about 0.01 µg/kg to about 100 µg/kg, from about 0.01 µg/kg to about 50 µg/kg, from about 0.01 µg/kg to about 20 µg/kg, from about 0.01 µg/kg to about 10 µg/kg, from about 0.01 µg/kg to about 5 µg/kg, from about 0.01 µg/kg to about 1 µg/kg, from about 0.05 µg/kg to about 1 µg/kg, or from about 0.1 µg/kg to about 1 µg/kg.

In some embodiments, the compound is administered at a dose of less than 0.01 µg/kg/day, less than 0.02 µg/kg/day, less than 0.05 µg/kg/day, less than 0.1 µg/kg/day, less than 0.2 µg/kg/day, less than 0.5 µg/kg/day, less than 1 µg/kg/day, less than 2 µg/kg/day, less than 5 µg/kg/day, less than 10 µg/kg/day, less than 20 µg/kg/day, less than 50 µg/kg/day, or less than 100 µg/kg/day. In other embodiments, the compound is administered at a dose of about 0.01 µg/kg/day, about 0.02 µg/kg/day, about 0.05 µg/kg/day, about 0.1 µg/kg/day, about 0.2 µg/kg/day, about 0.5 µg/kg/day, about 1 µg/kg/day, about 2 µg/kg/day, about 5 µg/kg/day, about 10 µg/kg/day, about 20 µg/kg/day, about 50 µg/kg/day, or about 100 µg/kg/day. In other embodiments, the compound is administered at a dose of from about 0.01 µg/kg/day to about 100 µg/kg/day, from about 0.01 µg/kg/day to about 50 µg/kg/day, from about 0.01 µg/kg/day to about 20 µg/kg/day, from about 0.01 µg/kg/day to about 10 µg/kg/day, from about 0.01 µg/kg/day to about 5 µg/kg/day, from about 0.01 µg/kg/day to about 1 µg/kg/day, from about 0.05 µg/kg/day to about 1 µg/kg/day, or from about 0.1 µg/kg/day to about 1 µg/kg/day.

In one embodiment, the compound is administered once daily (QD). In another embodiment, the compound is administered twice daily (BID). In another embodiment, the compound is administered three times daily (TID). In another embodiment, the compound is administered four times daily (QID).

In some embodiments, the subject has received previous treatment for a pulmonary or respiratory disease. In one embodiment, the subject has demonstrated progression on the previous treatment. In one embodiment, the subject has developed resistance to previous treatment. In some embodiments, the subject has received previous treatment for a pulmonary or respiratory disease and demonstrated progression on the previous treatment. In one embodiment, the previous treatment is steroid. In one embodiment, the steroid is dexamethasone.

In one embodiment, the subject is a mammal. In another embodiment, the subject is a human.

In one embodiment, the compound is Compound 1, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound. In another embodiment, the compound is a bis-hydrogensulfate salt of Compound 1. In another embodiment, the compound is crystalline Form 1 of the bis-hydrogensulfate salt of Compound 1. In one embodiment, Form 1 has an X-ray powder diffraction pattern comprising peaks at approximately 10.7, 12.4, and 23.6 degrees 2Θ. In one embodiment, Form 1 has an X-ray powder diffraction pattern further comprising peaks at approximately 19.2 and 20.4 degrees 2Θ.

In one embodiment, the compound is the free base of the compound of formula (I).
In one embodiment, the compound is a sulfuric acid salt of the compound of formula (I). In one embodiment, the compound is a bis-sulfuric acid salt, mono-sulfuric acid salt, or hemi-sulfuric acid salt of the compound of formula (I).

**ADMINISTRATION BY INHALATION**

Many diseases of the respiratory tract are known to respond to treatment by the direct application of therapeutic agents by inhalation. Such administration can result in the better utilization of the medicament in that the drug is deposited directly at the desired site and where its action may be required. Therefore, without being limited by a particular theory, administration by inhalation can significantly reduce the dose required to achieve therapeutic efficacy, which, in turn can result in marked reduction of undesired side effects and cost of medicament. In another embodiment, administration by inhalation delivers a compound to the lung without systemic exposure as in oral administration. It is typically accepted in the industry that the bioavailability of the drug is optimum when the drug particles delivered to the respiratory tract are between 1 to 5 microns in size.

Various methods and devices can be used to deliver a compound provided herein by inhalation. The inhalable formulation can be administered via the mouth or nose ultimately for pulmonary delivery thereof. For example, dry powder inhalers (DPIs), which usually have a means for introducing the drug (active drug plus carrier) into a high velocity air stream, can be used to practice the methods provided herein. The high velocity air stream is used as the primary mechanism for breaking up the cluster of micronized particles or separating the drug particles from the carrier. Inhalation devices useful for dispensing powder forms of medicament such as those described in U.S. Pat. Nos. 3,507,277; 3,518,992; 3,635,219; 3,795,244; and 3,807,400, are encompassed by the current disclosure. In certain embodiments, such devices also include propeller means, which upon inhalation aid in dispensing the powder out of the capsule, so that it is not necessary to rely solely on the inhaled air to suction powder from the capsule. (See, e.g., U.S. Pat. Nos. 2,517,482; 3,831,606; 3,948,264; and 5,458,135, all of which are incorporated herein by reference). In certain embodiments, utilization of vibration to facilitate suspension of power into an inhaled gas stream and which utilizes synthetic jetting to aerosolize drug powder from a blister pack is also provided herein. (See, e.g., U.S. Patent Nos. 7,318,434 and 7,334,577, incorporated herein by reference). In other embodiments, controlled aliquots or doses of a medication or pre-packaged drug in a blister pack, which includes a frangible crowned top element which can be conical, conical with a rounded point, rounded, such as those described in U.S. Patent No. 7,080,644, are also encompassed.

In certain embodiments, a compound provided herein is administered using Metered dose inhalers (MDIs). MDIs typically have a pressurized canister filled with a liquid propellant. The drug is either suspended or dissolved in the propellant. The MDIs have a metering valve for metering out a known quantity of the propellant and hence the drug. When the canister is depressurized against the MDI housing a known quantity of the propellant is discharged. The propellant evaporates leaving behind a fine aerosol of the drug suitable for inhalation by the patient. In certain embodiments, MDIs that contain a breath actuation mechanism a spacer are also encompassed herein.
In other embodiments, a compound provided herein is administered using nebulizers, such as the jet nebulizers. Nebulizers produce a fine aerosol mist/droplets which carry the drug either as a suspension or dissolved in the aqueous medium. The jet nebulizers use compressed air to atomize the aqueous solution. A drug can be administered to a patient with repetitive non-forced inhalation over a prolonged period of time.

Examples of devices suitable for such pulmonary delivery include, but are not limited to, air-jet, ultrasonic, or vibrating-mesh devices such as Pari LC Star, Aeroeclipse II, Prodisc (HaloLite), Acorn II, T Up-draft II, Sidestream, AeroTech II, Mini heart, MisterNeb, Sonix 2000, MABISMist II and other suitable aerosol systems. In some embodiments, the nebulizer is a vibrating-mesh nebulizer that could include an AERONEB PRO, AERONEB SOLO, AERONEB GO, AERONEB LAB, OMRON MICROAIR, PARI EFLOW, RESPIRONICS 1-NEB, or other suitable devices.

In certain circumstances, when inhalation cannot be used on, e.g., animals, direct instillation of a test material into the lungs via the trachea (intratracheal administration), is employed in studies as an alternative exposure procedure to inhalation. See Discroll, K. E., et al., Toxicological Sciences, 55, 24-35 (2000). Certain examples provided herein use intratracheal administration to evaluate the effects of the compounds provided herein on animals. Without being limited by any particular theory, intratracheal administration of a compound provided herein on animals such as rats and mice can be correlated with inhalation administration to humans.

FORMULATIONS FOR INHALATION

Also provided herein are formulations to be administered by inhalation. All types of inhalable formulation known in the art can be used in connection with methods provided herein.

In a dry powder inhaler, the dose to be administered is stored in the form of a non-pressurized dry powder and, on actuation of the inhaler, the particles of the powder are inhaled by the patient. Dry powder inhalers can be "passive" devices in which the patient's breath is the only source of gas which provides a motive force in the device, or "active" devices in which a source of compressed gas or alternative energy source is used. Formulations provided herein can be administered with either passive or active inhaler devices.

While it is desirable for as large a proportion as possible of the particles of active material to be delivered to the deep lung, it is usually preferable for as little as possible of the other components to penetrate the deep lung. Therefore, powders generally include particles of an active material, and carrier particles for carrying the particles of active material. The carrier particles can be composed of any pharmacologically inert material or combination of materials which is acceptable for inhalation. In some embodiments, carrier particles are composed of one or more crystalline sugars. In other embodiments, the carrier particles can be composed of one or more sugar alcohols or polyols. In other embodiments, the carrier particles are particles of dextrose or lactose. In some embodiments, the amount of carrier particles is up to 95%, up to 90%, up to 80%, or up to 50% by weight based on the total weight of the composition.
[0082] An additive material can also be provided in a dose which indicates to the patient that the dose has been administered. (See, e.g., WO 01/82906). The additive material, also referred to as indicator material, can be present in the powder as formulated for the dry powder inhaler, or be present in a separate form, such as in a separate location within the inhaler such that the additive becomes entrained in the airflow generated on inhalation simultaneously or sequentially with the powder containing the active material. Accordingly, provided herein is a formulation comprising a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with a carrier material.

[0083] Formulations provided herein, when inhaled, preferably exhibit a time to therapeutic effect of less than 3 hours, 2 hours, 1 hour, 30 minutes, 15 minutes, 10 minutes, or 5 minutes. In some embodiments, formulations provided herein, when inhaled, will have a therapeutic duration of about 1 to 48 hours.

[0084] In certain embodiments of the present invention, each dose is stored in a “blister” of a blister pack. In this regard, since an active agent may be susceptible to oxidation, it is sometimes important to prevent (or substantially limit) oxidation of the active agent prior to administration. Thus, in some embodiments, exposure of the formulation to air prior to administration is prevented by storing each dose in a sealed blister. In some embodiments, oxidation is further prevented (or limited) by placing a plurality of blisters into a further sealed container, such as a sealed bag made, for example of a foil such as aluminum foil. In some embodiments, the use of the sealed blisters (and optional sealed bags) can minimize the need to include anti-oxidants in the formulation.

[0085] In case of administration by a dry powder inhaler of the particles of active ingredient to the lung where they can be absorbed, the particle size characteristics of the powder are particularly important. In particular, for the effective delivery of active ingredient deep into the lung, the active particles should be small and well dispersed on actuation of the inhaler. In some embodiments, a fine particle fraction of at least 35% is generated on actuation of the inhaler device. In other embodiments, a fine particle fraction of at least 60%, at least 70%, or at least 80% is generated on actuation.

[0086] In certain embodiments, the formulation can also contain fine particles of an excipient material, which can be a material such as one of those referred to above as being suitable for use as a carrier material, for example, a crystalline sugar such as dextrose or lactose. The fine excipient material can be of the same or a different material from the carrier particles, where both are present. In certain embodiments, where any carrier particles and/or any fine excipient material present is of a material itself capable of inducing a sensation in the oropharyngeal region, the carrier particles and/or the fine excipient material can also be the indicator material. For example, the carrier particles and/or any fine particle excipient can comprise mannitol. In certain embodiments, the amount of fine excipient material, if present, can be up to 50%, up to 30%, or up to 20%, by weight, based on the total weight of the composition.

[0087] Formulations provided herein can also be formulated with additional excipients to aid delivery and release. In certain embodiments, powder can be formulated with relatively large carrier particles which aid the flow
properties of the powder. Examples of large carrier particles include, but are not limited to, lactose particles having
a mass medium aerodynamic diameter of greater than 90 microns. In other embodiments, hydrophobic
microparticles can be dispersed within a carrier material. For example, the hydrophobic microparticles can be
dispersed within a polysaccharide matrix, with the overall composition formulated as microparticles for direct
delivery to the lung. The polysaccharide acts as a further barrier to the immediate release of the active agent. This
can further aid the controlled release process. An example of a suitable polysaccharide is xanthan gum. Examples
of hydrophobic materials include, but are not limited to, solid state fatty acids such as oleic acid, lauric acid,
palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (e.g., esters and salts) thereof. Specific examples
of such materials include, but are not limited to, phosphatidylcholines, phosphatidylglycerols and other natural and
synthetic lung surfactants. In some embodiments, formulations provided herein contain metal stearates, in
particular magnesium stearate, which has been approved for delivery via the lung.

[0088] Formulations provided herein can also include one or more force control additives (FCAs) in addition to
the carrier and the active ingredient. In some embodiments, the FCAs can be provided in an amount from about
0.1% to about 10% by weight, from about 0.15% to 5% by weight, or from about 0.5% to about 2% by weight of
the total composition. In some embodiment, FCAs include, but are not limited to, anti-adherent materials. In other
embodiments, FCAs include, but are not limited to, magnesium stearate, leucine, lecithin, and sodium stearyl
fumarate, and those described in U.S. Pat. No. 6,153,224, which is hereby incorporated by reference.

[0089] In certain embodiments, formulations provided herein can be a "carrier free" formulation, which includes
only the active ingredient and one or more anti-adherents. Such carrier free formulations are described in WO
97/03649, the entire disclosure of which is hereby incorporated by reference.

[0090] As used herein, and unless otherwise specified, the term "anti-adherent material" refers to those additive
materials which will decrease the cohesion between the particles of the powder. Those materials will include, but
are not limited to, leucine and lecithin. In some embodiments, the anti-adherent material comprises an amino acid.
Amino acids have been found to provide, when present as anti-adherent material, high respirable fraction of the
active material and also good flow properties of the powder. In some embodiments, the amino acid is leucine, in
particular L-leucine. In other embodiments, the D- and DL-forms can also be used. The anti-adherent material can
comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, valine, methionine, cysteine,
phenylalanine. In other embodiments, the anti-adherent material can include magnesium stearate or colloidal
silicon dioxide.

[0091] In some embodiments, formulations provided herein are an aerosol formulation. In some embodiments,
the aerosol formulation can be contained in a canister. Examples of aerosol formulation include, but are not limited
to, an aerosol solution formulation and an aerosol suspension formulation. In certain embodiments, the aerosol
formulation can contain a compound provided herein, optionally in combination with other active ingredient(s), in a
propellant or in a propellant/solvent system and, optionally, further pharmaceutical acceptable additive or excipient.
In some embodiments, the formulations provided herein can be nebulized.
The propellant can be any pressure-liquefied propellant and is preferably a hydrofluoroalkane (HFA) or a mixture of different HFAs, including, but not limited to, HFA 134a (1,1,1,2-tetrafluoroethane), HFA 227 (1,1,2,3,3,3-heptafluoropropane), and mixtures thereof.

The solvent generally has a higher polarity than that of the propellant and can include one or more substances such as a pharmaceutically acceptable alcohol (e.g., ethanol), a polyol, such as propylene glycol or polyethylene glycol, or mixtures thereof. In some embodiments, the solvent is a lower branched or linear alkyl (C₁-, C₄) alcohols such as ethanol and isopropyl alcohol. In one embodiment, the co-solvent is ethanol.

In some embodiments, the active ingredient of the formulation is substantially completely and homogeneously dissolved in the propellant/solvent system, i.e., the formulation is a solution formulation. Optionally, the formulation can comprise other pharmaceutically acceptable additives or excipients, which are substantially inert materials that are non-toxic and do not interact in a negative manner with other components of the formulation. In some embodiments, the formulation can comprise one or more co-solvents, surfactants, carbohydrate, phospholipid, polymer, wetting agent, stabilizers, lubricants, or low volatility components.

In some embodiments, a suitable amount of an acid (organic or inorganic acid (mineral acids)) can be used as stabilizer. Examples include, but are not limited to, pharmaceutically acceptable monoprotic or polyprotic acid, such as: hydrogen halides (hydrochloric acid, hydrobromic acid, hydroiodic acid, etc.), phosphoric acid, nitric acid, sulphuric acid, and halogen oxoacids.

In other embodiments, low volatility components can be used in order to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles upon actuation of the inhaler and/or to improve the solubility of the active ingredient in the propellant/solvent system. In some embodiments, the low volatility component has a vapor pressure at 25°C lower than 0.1 kPa, or lower than 0.05 kPa. Examples of low-volatility components include, but are not limited to: esters such as isopropyl myristate, ascorbyl myristate, tocopherol esters; glycols such as propylene glycol, polyethylene glycol, glycerol; and surface active agents such as saturated organic carboxylic acids (e.g., lauric, myristic, stearic acid) and unsaturated carboxylic acids (e.g., oleic or ascorbic acid). The amount of low volatility component can vary from 0.1 to 10% w/w, from 0.5 to 5% (w/w), or from 1 to 2% (w/w).

In other embodiments, water at an amount between 0.005 and 0.3% (w/w) can be added to the formulations in order to favorably affect the solubility of the active ingredient without increasing the MMAD of the aerosol droplets upon actuation.

**PULMONARY OR RESPIRATORY DISEASES**

Provided herein is a method of treating, preventing, and/or managing pulmonary or respiratory disease using a compound provided herein. Examples of pulmonary or respiratory disease include, but are not limited to, lung inflammation, chronic obstructive pulmonary disease, asthma, pneumonia, hypersensitivity pneumonitis,
pulmonary infiltrate with eosinophilia, environmental lung disease, pneumonia, bronchiectasis, cystic fibrosis, interstitial lung disease, post inflammatory pulmonary fibrosis, primary pulmonary hypertension, pulmonary thromboembolism, disorders of the pleura, disorders of the mediastinum, disorders of the diaphragm, disorders of the larynx, disorders of the trachea, acute lung injury, hypoventilation, hyperventilation, sleep apnea, acute respiratory distress syndrome, mesothelioma, sarcoma, graft rejection, graft versus host disease, lung cancer, allergic rhinitis, allergy, allergic bronchopulmonary aspergillosis, asbestosis, aspergillosis, aspergillosis, bronchiectasis, chronic bronchitis, emphysema, eosinophilic pneumonia, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, non-specific interstitial pneumonia(NSIP), bronchiolitis obliterans with organizing pneumonia (BOOP, also called cryptogenic organizing pneumonia or COP), lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonitis invasive pneumococcal disease, pneumococcal pneumonia, influenza, nontuberculous mycobacteria, pleural effusion, a pleural cavity disease, empyema, pleurisy, pneumocooniosis, pneumocytosis, respiratory viral infection, acute bronchitis, aspiration pneumonia, ventilator-associated pneumonia, pneumocystic jiroveci pneumonia, pneumonia, pulmonary actinomycosis, pulmonary alveolar proteinosis, pulmonary anthrax, pulmonary edema, pulmonary embolus, pulmonary embolism, acute chest syndrome, idiopathic pulmonary hemosiderosis, pulmonary hemorrhage, pulmonary hyperplasia, pulmonary inflammation, pulmonary histiocytosis X, eosinophilic granuloma, pulmonary Langerhan's cell histiocytosis, occupational lung disease, pneumopathy due to inhalation of dust, respiratory conditions due to chemical fumes and vapors, lipoid pneumonia, pulmonary hypertension, pulmonary arterial hypertension, pulmonary nocardiosis, pulmonary tuberculosis, pulmonary veno-occlusive disease, pulmonary vascular disease, rheumatoid lung disease, connective tissue disease-associated interstitial lung disease (e.g., systemic sclerosis (SSc or scleroderma)-associated interstitial lung disease, polymyositis-associated interstitial lung disease, dermatomyositis-associated interstitial lung disease, rheumatoid arthritis- associated interstitial lung disease, systemic lupus erythematosus-associated interstitial lung disease, interstitial lung disease associated with Sjogren's syndrome, mixed connective tissue disease-associated interstitial lung disease, and ankylosing spondylitis-associated interstitial lung disease), a restrictive lung disease, a respiratory tract infection (upper and lower), sarcoidosis, Wegener's granulomatosis (also known as granulomatosis with polyangiitis (GPA) or necrotizing granulomatous vasculitis (NGV)), Churg-Strauss Syndrome, microscopic polyangiitis (MPA), small cell lung carcinoma, non-small cell lung carcinoma, lymphangioleiomyomatosis (LAM), radiation-induced lung disease (also known as radiation pneumonitis), pulmonary vasculitis, viral pneumonia, pneumococcal pneumonia, bacterial pneumonia, bronchopneumonia, epithelial tumors, papillomas, adenomas, squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma, adenosquamous carcinoma, carcinoid tumor, carcinoma of salivary-gland type, soft tissue tumors, localized fibrous tumor, epithelioid hemangioendothelioma, pleuropulmonary blastoma, chondroma, calcifying fibrous pseudotumor of the pleura, congenital peribronchial myofibroblastic tumor, diffuse pulmonary lymphangiomatosis, desmoplastic small round cell tumor, mesothelial tumors, adenomatoid tumor, epithelioid mesothelioma, sarcomatoid mesothelioma, biphasic mesothelioma, hamartoma, sclerosing hemangioma, clear cell tumor, germ cell neoplasms, thymoma, melanoma,
and secondary tumor. In certain embodiments, provided herein is a method of treating, preventing, and/or managing a lymphoproliferative disease using a compound provided herein. Examples of lymphoproliferative disease include, but are not limited to, lymphoid interstitial pneumonia, nodular lymphoid hyperplasia, and lymphomatoid granulomatosis.

[00100] In certain embodiments, the pulmonary or respiratory disease to be treated, prevented and/or managed using a compound provided herein is an obstructive lung disease or disorder. In some embodiments, the obstructive lung disease is acute respiratory distress syndrome (ARDS), asthma, bronchiectasis, bronchiolectasis, bronchiolitis, bronchitis, chronic obstructive pulmonary disease (COPD), or emphysema.

[00101] In one embodiment, the pulmonary or respiratory disease is relapsed or refractory. In one embodiment, the pulmonary disease is relapsed. In one embodiment, the pulmonary disease is refractory. In one embodiment, the respiratory disease is relapsed. In one embodiment, the respiratory disease is refractory.

[00102] In certain embodiments, in treating, preventing and/or managing a pulmonary or respiratory disease provided herein, a therapeutically or prophylactically effective amount of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.005 to about 1.000 mg per day, from about 0.01 to about 500 mg per day, from about 0.01 to about 250 mg per day, from about 0.01 to about 100 mg per day, from about 0.1 to about 100 mg per day, from about 0.5 to about 100 mg per day, from about 1 to about 100 mg per day, from about 0.01 to about 50 mg per day, from about 0.1 to about 50 mg per day, from about 0.5 to about 50 mg per day, from about 1 to about 50 mg per day, from about 2 to about 25 mg per day, or from about 5 to about 10 mg per day.

[00103] In certain embodiments, the therapeutically or prophylactically effective amount is about 0.1, about 0.2, about 0.5, about 1, about 2, about 5, about 10, about 15, about 20, about 25, about 30, about 40, about 45, about 50, about 60, about 70, about 80, about 90, about 100, or about 150 mg per day.

[00104] In one embodiment, the recommended daily dose range of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, for the conditions described herein lie within the range of from about 0.5 mg to about 50 mg per day, in a single once-a-day dose or in divided doses throughout a day. In some embodiments, the dosage ranges from about 1 mg to about 50 mg per day. In other embodiments, the dosage ranges from about 0.5 to about 5 mg per day. Specific doses per day include 0.1, 0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 mg per day.

[00105] In one embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered at a dose of less than 0.1, about 0.1, less than 0.5, about 0.5, between about 0.1 and about 1.0, between about 0.5 and about 1.0, about 1, or about 2 mg per day.
In another embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered at a dose of less than 0.2, about 0.2, less than 1.0, about 1.0, between about 0.2 and about 2.0, between about 1.0 and about 2.0, about 2, or about 4 mg per day.

In another embodiment, the dose is less than 0.1 mg per day.

In another embodiment, the dose is about 0.1 mg per day.

In another embodiment, the dose is less than 0.5 mg per day.

In another embodiment, the dose is about 0.5 mg per day.

In another embodiment, the dose is between about 0.1 and about 1.0 mg per day.

In another embodiment, the dose is between about 0.5 and about 1.0 mg per day.

In another embodiment, the dose is about 1 mg per day.

In another embodiment, the dose is about 2 mg per day.

In another embodiment, the dose is less than 0.2 mg per day.

In another embodiment, the dose is about 0.2 mg per day.

In another embodiment, the dose is less than 1.0 mg per day.

In another embodiment, the dose is about 1.0 mg per day.

In another embodiment, the dose is between about 0.2 and about 2.0 mg per day.

In another embodiment, the dose is between about 1.0 and about 2.0 mg per day.

In another embodiment, the dose is about 2 mg per day.

In another embodiment, the dose is about 4 mg per day.

In a specific embodiment, the recommended starting dosage can be 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 25 or 50 mg per day. In another embodiment, the recommended starting dosage can be 0.5, 1, 2, 3, 4, or 5 mg per day. The dose can be escalated to 15, 20, 25, 30, 35, 40, 45 and 50 mg/day.

In certain embodiments, the therapeutically or prophylactically effective amount is from about 0.0001 to about 100 mg/kg/day, 0.001 to about 100 mg/kg/day, from about 0.01 to about 50 mg/kg/day, from about 0.01 to about 25 mg/kg/day, from about 0.01 to about 10 mg/kg/day, from about 0.01 to about 9 mg/kg/day, 0.01 to about 8 mg/kg/day, from about 0.01 to about 7 mg/kg/day, from about 0.01 to about 6 mg/kg/day, from about 0.01 to about 5 mg/kg/day, from about 0.01 to about 4 mg/kg/day, from about 0.01 to about 3 mg/kg/day, from about 0.01 to about 2 mg/kg/day, or from about 0.01 to about 1 mg/kg/day.

In certain embodiments, the therapeutically or prophylactically effective amount is from about 0.0001 to about 10 mg/kg/day, from about 0.0001 to about 5 mg/kg/day, from about 0.0001 to about 1 mg/kg/day, from about 0.001 to about 10 mg/kg/day, from about 0.01 to about 10 mg/kg/day, from about 0.05 to about 10 mg/kg/day, from about 0.1 to about 10 mg/kg/day, or from about 1 to about 10 mg/kg/day. In one embodiment, the compound provided herein is administered intratracheally and the effective amount is from about 0.0001 to about 10 mg/kg/day, from about 0.0001 to about 5 mg/kg/day, from about 0.0001 to about 1 mg/kg/day, from about 0.001 to
about 10 mg/kg/day, from about 0.01 to about 10 mg/kg/day, from about 0.05 to about 10 mg/kg/day, from about 0.1 to about 10 mg/kg/day, or from about 1 to about 10 mg/kg/day. In another embodiment, the compound provided herein is administered orally and the effective amount is from about 0.0001 to about 10 mg/kg/day, from about 0.0001 to about 5 mg/kg/day, from about 0.0001 to about 1 mg/kg/day, from about 0.001 to about 10 mg/kg/day, from about 0.01 to about 10 mg/kg/day, from about 0.05 to about 10 mg/kg/day, from about 0.1 to about 10 mg/kg/day, or from about 1 to about 10 mg/kg/day. In one embodiment, the compound provided herein is administered intratracheally and the effective amount is from about 0.0001 to about 10 mg/kg/day. In another embodiment, the compound provided herein is administered orally and the effective amount is from about 0.1 to about 10 mg/kg/day.

[00126] The administered dose can also be expressed in units other than mg/kg/day. For example, doses for parenteral administration can be expressed as mg/m²/day. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to mg/m²/day to given either the height or weight of a subject or both (see, www.fda.gov/cder/cancer/animalframe.htm). For example, a dose of 1 mg/kg/day for a 65 kg human is approximately equal to 37 mg/m²/day.

[00127] A compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). In addition, the administration can be continuous (i.e., daily for consecutive days or every day), intermittent, e.g., in cycles (i.e., including days, weeks, or months of rest without drug). As used herein, the term "daily" is intended to mean that a therapeutic compound, such as Compound 1, is administered once or more than once each day, for example, for a period of time. The term "continuous" is intended to mean that a therapeutic compound, such as Compound 1, is administered daily for an uninterrupted period of at least 10 days to 52 weeks. The term "intermittent" or "intermittently" as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of Compound 1 is administration for one to six days per week, administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days. The term "cycling" as used herein is intended to mean that a therapeutic compound, such as Compound 1, is administered daily or continuously but with a rest period.

[00128] In some embodiments, the frequency of administration is in the range of about a daily dose to about a monthly dose. In certain embodiments, administration is once a day, twice a day, three times a day, four times a day, once every other day, twice a week, once every week, once every two weeks, once every three weeks, or once every four weeks. In one embodiment, the compound provided herein is administered three times a day. In another embodiment, the compound provided herein is administered twice a day. In yet another embodiment, the compound provided herein is administered four times a day.
In one embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered twice per day (BID). In one embodiment, the dose is about 0.1, 0.2, 0.25, 0.5, 1, 2, 2.5, 5, 10, 15, 20, 25, or 50 mg BID.

In one embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered at a dose of less than 0.1, about 0.1, less than 0.5, about 0.5, between about 0.1 and about 1.0, between about 0.5 and about 1.0, about 1, or about 2 mg BID.

In another embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered at a dose of less than 0.2, about 0.2, less than 1.0, about 1.0, between about 0.2 and about 2.0, between about 1.0 and about 2.0, about 2, or about 4 mg BID.

In one embodiment, the dose is less than 0.1 mg BID.

In another embodiment, the dose is about 0.1 mg BID.

In another embodiment, the dose is less than 0.5 mg BID.

In another embodiment, the dose is about 0.5 mg BID.

In another embodiment, the dose is between about 0.1 and about 1.0 mg BID.

In another embodiment, the dose is between about 0.5 and about 1.0 mg BID.

In another embodiment, the dose is about 1 mg BID.

In another embodiment, the dose is about 2 mg BID.

In another embodiment, the dose is less than 0.2 mg BID.

In another embodiment, the dose is about 0.2 mg BID.

In another embodiment, the dose is less than 1.0 mg BID.

In another embodiment, the dose is about 1.0 mg BID.

In another embodiment, the dose is between about 0.2 and about 2.0 mg BID.

In another embodiment, the dose is between about 1.0 and about 2.0 mg BID.

In another embodiment, the dose is about 2 mg BID.

In another embodiment, the dose is about 4 mg BID.

In one embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once daily (QD). In one embodiment, the dose is about 0.1, 0.2, 0.25, 0.5, 1, 2, 2.5, 5, 10, 15, 20, 25, or 50 mg QD.

In one embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph
thereof, is administered at a dose of less than 0.1, about 0.1, less than 0.5, about 0.5, between about 0.1 and about 1.0, between about 0.5 and about 1.0, about 1, or about 2 mg QD.

[00150] In another embodiment, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered at a dose of less than 0.2, about 0.2, less than 1.0, about 1.0, between about 0.2 and about 2.0, between about 0.5 and about 2.0, about 2, or about 4 mg QD.

[00151] In one embodiment, the dose is less than 0.1 mg QD.
[00152] In another embodiment, the dose is about 0.1 mg QD.
[00153] In another embodiment, the dose is less than 0.5 mg QD.
[00154] In another embodiment, the dose is about 0.5 mg QD.
[00155] In another embodiment, the dose is between about 0.1 and about 1.0 mg QD.
[00156] In another embodiment, the dose is between about 0.5 and about 1.0 mg QD.
[00157] In another embodiment, the dose is about 1 mg QD.
[00158] In another embodiment, the dose is about 2 mg QD.
[00159] In another embodiment, the dose is less than 0.2 mg QD.
[00160] In another embodiment, the dose is about 0.2 mg QD.
[00161] In another embodiment, the dose is less than 1.0 mg QD.
[00162] In another embodiment, the dose is about 1.0 mg QD.
[00163] In another embodiment, the dose is between about 0.2 and about 2.0 mg QD.
[00164] In another embodiment, the dose is between about 1.0 and about 2.0 mg QD.
[00165] In another embodiment, the dose is about 2 mg QD.
[00166] In another embodiment, the dose is about 4 mg QD.
[00167] In one embodiment, the amount of the compound administered is sufficient to provide a lung concentration of the compound at steady state, ranging from about 0.005 to about 100 µM, from about 0.005 to about 10 µM, from about 0.01 to about 10 µM, from about 0.01 to about 5 µM, from about 0.005 to about 1 µM, from about 0.005 to about 0.5 µM, from about 0.005 to about 0.5 µM, from about 0.01 to about 0.2 µM, or from about 0.01 to about 0.1 µM. In one embodiment, the amount of the compound administered is sufficient to provide a lung concentration at steady state, of about 0.005 to about 100 µM. In another embodiment, the amount of the compound administered is sufficient to provide a lung concentration at steady state, of about 0.005 to about 10 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a lung concentration at steady state, of about 0.01 to about 10 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a lung concentration at steady state, of about 0.01 to about 5 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a lung concentration at steady state, of about 0.005 to about 1 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a lung concentration at steady state, of about 0.005 to about 0.5 µM. In yet another
embodiment, the amount of the compound administered is sufficient to provide a lung concentration of the compound at steady state, of about 0.01 to about 0.2 µM. In still another embodiment, the amount of the compound administered is sufficient to provide a lung concentration of the compound at steady state, of about 0.01 to about 0.1 µM. As used herein, the term "lung concentration at steady state" is the concentration reached when the rate of drug administration is equal to rate of drug elimination from the lung. Once steady state is reached, there are minor peaks and troughs on the time dependent curve of the lung concentration of the compound.

[00168] In one embodiment, the amount administered is sufficient to provide a maximum lung concentration (peak concentration) of the compound, ranging from about 0.005 to about 100 µM, from about 0.005 to about 10 µM, from about 0.01 to about 10 µM, from about 0.01 to about 5 µM, from about 0.005 to about 1 µM, from about 0.005 to about 0.5 µM, from about 0.01 to about 0.2 µM, or from about 0.01 to about 0.1 µM. In one embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.005 to about 100 µM. In another embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.005 to about 10 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.01 to about 10 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.01 to about 5 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.005 to about 5 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.005 to about 0.5 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.01 to about 0.2 µM. In still another embodiment, the amount of the compound administered is sufficient to provide a maximum lung concentration of the compound of about 0.01 to about 0.1 µM.

[00169] In one embodiment, the amount administered is sufficient to provide a minimum lung concentration (trough concentration) of the compound, ranging from about 0.005 to about 100 µM, from about 0.005 to about 10 µM, from about 0.01 to about 10 µM, from about 0.01 to about 5 µM, from about 0.005 to about 1 µM, from about 0.005 to about 0.5 µM, from about 0.01 to about 0.2 µM, or from about 0.01 to about 0.1 µM, when more than one doses are administered. In one embodiment, the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.005 to about 100 µM. In another embodiment, the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.005 to about 10 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.01 to about 10 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.01 to about 5 µM. In yet another embodiment, the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.005 to about 1 µM. In yet another embodiment,
the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.005 to about 0.5 μM. In yet another embodiment, the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.01 to about 0.2 μM. In still another embodiment, the amount of the compound administered is sufficient to provide a minimum lung concentration of the compound of about 0.01 to about 0.1 μM.

[00170] In one embodiment, the amount administered is sufficient to provide an area under the curve (AUC) of the compound, ranging from about 50 to about 10,000 ng*hr/mL, about 100 to about 50,000 ng*hr/mL, from about 100 to 25,000 ng*hr/mL, or from about 10,000 to 25,000 ng*hr/mL.

[00171] In certain embodiments, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day from one day to six months, from one week to three months, from one week to four weeks, from one week to three weeks, or from one week to two weeks. In certain embodiments, the compound provided herein is administered once per day for one week, two weeks, three weeks, or four weeks. In one embodiment, the compound provided herein is administered once per day for one week. In another embodiment, the compound provided herein is administered once per day for two weeks. In yet another embodiment, the compound provided herein is administered once per day for three weeks. In still another embodiment, the compound provided herein is administered once per day for four weeks.

[00172] In certain embodiments, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered twice per day from one day to six months, from one week to three months, from one week to four weeks, from one week to three weeks, or from one week to two weeks. In certain embodiments, the compound provided herein is administered twice per day for one week, two weeks, three weeks, or four weeks. In one embodiment, the compound provided herein is administered twice per day for one week. In another embodiment, the compound provided herein is administered twice per day for two weeks. In yet another embodiment, the compound provided herein is administered twice per day for three weeks. In still another embodiment, the compound provided herein is administered twice per day for four weeks.

[00173] The compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, can be delivered as a single dose such as, e.g., a single bolus injection, or oral tablets or pills; or over time, such as, e.g., continuous infusion over time or divided bolus doses over time. The compound can be administered repeatedly if necessary, for example, until the patient experiences stable disease or regression, or until the patient experiences disease progression or unacceptable toxicity.
Chronic Obstructive Pulmonary Disease

[00174] In one embodiment, said obstructive lung disease or disorder is chronic obstructive pulmonary disease (COPD), e.g., as diagnosed by a forced expiratory air volume in 1 second (FEVi) to forced vital capacity (FVC) ratio of less than 0.7. In another embodiment, administration of a compound provided herein results in a detectable rise in the FEVi/FEC ratio above 0.7 after administration, e.g., a rise of 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, or more or more.

[00175] In one embodiment, provided herein is a method of reducing a COPD associated symptom in a subject, comprising administering a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, by inhalation in an amount sufficient to reduce the COPD associated symptom. In one embodiment, the subject is a mammalian subject, e.g., an animal model or as part of therapeutic protocol. In one embodiment, the compound is used as a single agent or in combination with another agent or therapeutic modality.

[00176] In one embodiment, provided herein is a method of treating, preventing, and/or managing COPD in a subject, comprising administering an effective amount of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, to a subject in need thereof by inhalation. In one embodiment, the compound is administered as a single agent. In another embodiment, the compound is administered in combination with another agent or therapeutic modality.

[00177] As used herein, and unless otherwise specified, "COPD" or a "symptom" associated with COPD encompasses all types of manifestation of COPD as disclosed herein or as known in the art. Examples of COPD include, but are not limited to, emphysema, chronic bronchitis, and bronchiectasis. Examples of symptom of COPD include, but are not limited to, wheezing, coughing, chest tightness, shortness of breath, difficulty in breathing, coughing up mucus/phlegm, and use of accessory muscle. Symptoms are often worse at night or in the early morning, or in response to exercise or cold air. In one embodiment, the symptom of asthma is shortness of breath or difficulty in breathing.

[00178] As used herein, and unless otherwise specified, to "decrease," "ameliorate," "reduce," "inhibit," "treat" (or the like) COPD or a symptom associated with COPD includes reducing (or preventing an increase in) the severity and/or frequency of one or more symptoms of COPD, as well as preventing COPD and/or one or more symptoms of COPD (e.g., by reducing (or preventing an increase in) the severity and/or frequency of flares of symptoms). In the context of biological molecules, to "decrease", "ameliorate," "reduce," "inhibit," or the like, includes decreasing the level (e.g., the level, e.g., of mRNA or protein, that can be measured in a biological sample) or the activity (e.g., the function) of the molecule.

[00179] In some embodiments, the symptom is reduced by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%
relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the pre-treatment level in the sample or subject treated, or it can be the level in a control population (e.g., the level in subjects who do not have COPD or the level in samples derived from subjects who do not have COPD). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

[00180] In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

[00181] In certain embodiments, the subject is an animal model of COPD, a human with COPD, or a subject (e.g., a human) at risk for developing COPD. In some embodiments, the subject is a human who has a family history of COPD, who carries a gene associated with COPD, who is positive for a biomarker associated with COPD, or a combination thereof. In some embodiments, the subject has been diagnosed with COPD. In some embodiments, the subject has one or more signs or symptoms associated with COPD. In some embodiments, the subject is at risk for developing COPD (e.g., the subject carries a gene that, individually, or in combination with other genes or environmental factors, is associated with development of COPD).

[00182] In one embodiment, the subject has been previously diagnosed of COPD or has episodic symptoms of airflow obstruction (e.g., shortness of breath, wheezing and/or chest tightness) for at least 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, 12 months before a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered. In one embodiment, the subject has been previously diagnosed of COPD or has episodic symptoms of airflow obstruction (e.g., wheezing and/or chest tightness) for at least 6 months before a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered.

[00183] In some embodiments, the subject has been previously treated for COPD. In some embodiments, the subject has been previously treated for COPD but are non-responsive to standard therapies. Thus, in one embodiment, provided herein is a method of treating, preventing, and/or managing COPD in a subject, comprising administering an effective amount of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, to a subject in need thereof, wherein the subject has been previously administered a therapy for COPD.

[00184] In some embodiments, the subject has not been previously treated for COPD.

[00185] In one embodiment, without being limited by any particular theory, administering an effective amount of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, does not result in, or results in reduced, one or more common side effects of COPD treatment. The common side effects of COPD treatment include, but are not limited to: allergic reactions such as rashes, hives, swelling of the face, mouth and
tongue, and breathing problems; sudden breathing problems; effects on heart such as increased blood pressure, fast and irregular heart beat, and chest pain; effects on nervous system such as tremor and nervousness; reduced adrenal function; changes in blood contents; weakened immune system and higher chance of infections; lower bone mineral density; eye problems such as glaucoma and cataracts; slowed growth in children; pneumonia; thrush in the mouth and throat; throat irritation; hoarseness and voice changes; viral respiratory infections; headache; and muscle and bone pain.

[00186] In some embodiments, the side effect is reduced by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the side effect level in the subject treated with other COPD therapies (e.g., albuterol, levalbuterol, ipratropium, tiotropium, terbutaline, theophylline, formoterol, salmeterol, flucaltisone, methylprednisone, and prednisone). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

Asthma

[00187] In another specific embodiment, said obstructive lung disease or disorder is asthma. In other embodiments, administration of a compound provided herein results in a detectable improvement in one or more symptoms of asthma, e.g., airway obstruction, as determined by spirometry or a peak flow meter.

[00188] In one embodiment, provided herein is a method of reducing an asthma associated symptom in a subject, comprising administering a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, by inhalation in an amount sufficient to reduce the asthma associated symptom. In one embodiment, the subject is a mammalian subject, e.g., an animal model or as part of therapeutic protocol. In one embodiment, the compound is used as a single agent or in combination with another agent or therapeutic modality.

[00189] In one embodiment, provided herein is a method of treating, preventing, and/or managing asthma in a subject, comprising administering an effective amount of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof to a subject in need thereof by inhalation. In one embodiment, the compound is administered as a single agent. In another embodiment, the compound is administered in combination with another agent or therapeutic modality.

[00190] As used herein, and unless otherwise specified, "asthma" or a "symptom" associated with asthma encompasses all types of manifestation of asthma as disclosed herein or as known in the art. Examples of asthma include, but are not limited to, severe and/or refractory asthma, atopic (extrinsic) asthma, non-atopic (intrinsic) asthma, mixed atopic and non-atopic asthma, cold-induced asthma, type 1 brittle asthma, type 2 brittle asthma,
asthma attack, status asthmaticus, exercise-induced asthma, or occupational asthma. In one embodiment, the asthma is severe or refractory asthma. Examples of symptom of asthma include, but are not limited to, wheezing, coughing, chest tightness, shortness of breath, and use of accessory muscle. Symptoms are often worse at night or in the early morning, or in response to exercise or cold air. Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV₁), and peak expiratory flow rate. In one embodiment, the symptom of asthma is wheezing or chest tightness. In some embodiments, the asthma effects can be assessed in the late asthmatic response (LAR).

[00191] As used herein, and unless otherwise specified, "asthma" or a "symptom" associated with asthma also encompasses biological concomitants of asthma as disclosed herein or as known in the art. Examples include, but are not limited to, immune complexes, elevated levels of cytokines (e.g., interferons (e.g., Type I interferons, e.g., IFN-a and/or IFN-β); interleukins (e.g., IL-6, IL-8, IL-1, and IL-18) and TNF-a), elevated levels of anti-dsDNA autoantibodies, overexpression of IFN-a and/or IFN-β inducible genes, elevated levels of IP-10, elevated levels of sCD40L, reduced levels of C3-derived C3b, reduced peripheral iNKT cell frequencies, defective B cell-mediated stimulation of iNKT cells, altered CD1d expression on B cells, reduced numbers of natural regulatory T cells (Treg), altered level of C-reactive protein, overexpression of mRNA for IL-4, overexpression of mRNA for IL-21, and elevated serum anti-collagen level. In some embodiments, the symptom is overexpression of IFN-a, TNF-a, IL-6, IL-8, or IL-1. In one embodiment, the symptom is overexpression of IFN-a. In one embodiment, the symptom is overexpression of IL-6. In some embodiments, the symptom is overexpression of mRNA for IL-4 or overexpression of mRNA for IL-21. In some embodiments, the symptom is elevated serum anti-collagen level.

[00192] As used herein, and unless otherwise specified, to "decrease," "ameliorate," "reduce," "inhibit," "treat" (or the like) asthma or a symptom associated with asthma includes reducing (or preventing an increase in) the severity and/or frequency of one or more symptoms of asthma, as well as preventing asthma and/or one or more symptoms of asthma (e.g., by reducing (or preventing an increase in) the severity and/or frequency of flares of symptoms). In the context of biological molecules, to "decrease", "ameliorate," "reduce," "inhibit," or the like, includes decreasing the level (e.g., the level, e.g., of mRNA or protein, that can be measured in a biological sample) or the activity (e.g., the function) of the molecule.

[00193] In some embodiments, the symptom is reduced by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the pre-treatment level in the sample or subject treated, or it can be the level in a control population (e.g., the level in subjects who do not have asthma or the level in samples derived from subjects who do not have asthma). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

[00194] In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.
In certain embodiments, the subject is an animal model of asthma, a human with asthma, or a subject (e.g., a human) at risk for developing asthma. In some embodiments, the subject is a human who has a family history of asthma, who carries a gene associated with asthma, who is positive for a biomarker associated with asthma, or a combination thereof. In some embodiments, the subject has been diagnosed with asthma. In some embodiments, the subject has one or more signs or symptoms associated with asthma. In some embodiments, the subject is at risk for developing asthma (e.g., the subject carries a gene that, individually, or in combination with other genes or environmental factors, is associated with development of asthma).

In one embodiment, the subject has been previously diagnosed of asthma or has episodic symptoms of airflow obstruction (e.g., wheezing and/or chest tightness) for at least 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, 12 months before a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered. In one embodiment, the subject has been previously diagnosed of asthma or has episodic symptoms of airflow obstruction (e.g., wheezing and/or chest tightness) for at least 6 months before a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered.

In one embodiment, the subject has a forced expiratory volume in one second (FEVi) value of at least 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50% of a control value. In one embodiment, the subject has a forced expiratory volume in one second (FEVi) value of at least 70% of a control value. In one embodiment, the control value may be calculated based on American Thoracic Society (ATS)/European Respiratory Society (ERS) standards.

In one embodiment, the subject has a positive response to a skin prick test to an allergen. In one embodiment, the positive response means that the induration of skin test wheal is larger in diameter (e.g., at least 2 mm larger) than the diameter of the control wheal. The allergen can be any allergen provided herein or known in the art that can be used in the diagnosis or determining status of asthma.

In one embodiment, the subject has an early-phase asthmatic response (EAR) of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% to an inhaled allergen challenge. In one embodiment, the subject has an early-phase asthmatic response of at least 20% to an inhaled allergen challenge. In one embodiment, the EAR response is a decrease from pre-challenge in FEVi on 2 consecutive occasions within 0 to 3 hours of last allergen challenge.

In one embodiment, the subject has a late-phase asthmatic response (LAR) of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% to an inhaled allergen challenge. In one embodiment, the subject has a late-phase asthmatic response of at least 15% to an inhaled allergen challenge. In one embodiment, the LAR response is a decrease from pre-challenge in FEVi on 2 consecutive occasions within 3 to 10 hours of last allergen challenge.
In one embodiment, the subject has an early-phase asthmatic response of at least 20% and a late-phase asthmatic response of at least 15% to an inhaled allergen challenge. The inhaled allergen can be any inhaled allergen provided herein or known in the art that can be used in the diagnosis or determining status of asthma.

In one embodiment, the subject exhibits an elevated level of C-reactive protein. In one embodiment, the subject exhibits an elevated level of C-reactive protein of at least 1.0 mg/L. In one embodiment, the subject exhibits an elevated level of C-reactive protein of at least 7 mg/L.

In some embodiments, the subject exhibits elevated levels of antinuclear antibodies (e.g., anti-Smith antibodies, anti-double stranded DNA (dsDNA) antibodies, anti-U1 RNP, SS-a (or anti-Ro), SS-b (or anti-La)), antiphospholipid antibodies, anti-ss DNA antibodies, anti-histone antibodies, or anticardiolipin antibodies. In some embodiments, the subject exhibits elevated levels of anti-dsDNA antibodies. In some embodiments, the subject exhibits elevated levels of anti-Sm antibodies.

In some embodiments, the subject exhibits autoantibodies against one or more antigens that are known to be associated with asthma or with asthma subtypes. In some embodiments, the subject exhibits autoantibodies against Sm/anti-RNP or Ro/La autoantigens.

The levels of antibodies associated with asthma can be assessed using methods known in the art, e.g., indirect immunofluorescence. In some embodiments, the methods disclosed herein reduce or prevent an increase in the levels of one or more of the foregoing antibodies.

In some embodiments, the subject exhibits elevated levels of IFN-α, TNF-α, IL-6, IL-8, or IL-1. In one embodiment, the subject exhibits an elevated level of IFN-α. In another embodiment, the subject exhibits an elevated level of IL-6. In another embodiment, the subject exhibits an elevated level of mRNA for IL-4 or IL-21.

In some embodiments, the subject has a mutation (e.g., an SNP) in a gene associated with asthma. In one embodiment, the gene is selected from STAT4, IRF5, BANK1, ITGAM, PD1, FAM167A-BLK, IRF5-TNP03, KIAA1542, TNFAIP3, XKR6, lq25.1, PXK, ATG5, ICAI, XKR6, LYN and SCUB2 or a combination thereof. In some embodiments, the subject carries the DR3 and DQ2 variants, or the DR2 and DQ6 variants of HLA class II genes. In some embodiments, the subject has a deficiency in one or more complement proteins, e.g., a deficiency of a complement protein coded by the C4A or C2 genes on chromosome 6, or theClr and Cls genes on chromosome 12.

In some embodiments, the subject exhibits excessive PI3K activity or abnormal activity (e.g., excessive or reduced activity) of one or more components of the PI3K signaling pathway (e.g., Akt (PKB), mTOR, a Tec kinase (e.g., Btk, Itk, Tec), phospholipase C, PDK1, PKCs, NFKB, Rac GEF (e.g., Vav-1), or Rac).

In some embodiments, the subject is an animal model of asthma provided herein or known in the art. Examples include, but are not limited to, the murine lipopolysaccharide (LPS) induced pulmonary inflammation model, the murine ovalbumin-induced allergic airway inflammation model, and the rat-LPS model of asthma.

In some embodiments, the subject has been previously treated for asthma. In some embodiments, the subject has been previously treated for asthma but are non-responsive to standard therapies. Thus, in one
embodiment, provided herein is a method of treating, preventing, and/or managing asthma in a subject, comprising administering an effective amount of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, to a subject in need thereof, wherein the subject has been previously administered a therapy for asthma.

[00211] In some embodiments, the subject has not been previously treated for asthma.

[00212] In one embodiment, without being limited by any particular theory, administering an effective amount of a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, does not result in, or results in reduced, one or more common side effects of asthma treatment. The common side effects of asthma treatment include, but are not limited to, poor growth, decreased bone density, disseminated varicella infection (chickenpox that spreads to organs), easy bruising, cataracts, glaucoma, adrenal gland suppression, stomach upset, headache, liver test abnormalities, skin rashes, Churg Strauss syndrome, bad taste in month, cough, itching, sore throat, sneezing, stuffy nose, viral illness, upper respiratory tract infections, sinusitis, feeling dizzy or faint, hives, changes in voice, swelling of the tongue, or difficulty in swallowing.

[00213] In some embodiments, the side effect is reduced by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the side effect level in the subject treated with other asthma therapies (e.g., Xolair, Cromolyn Sodium, Nedocromil, Montelukast, and prednisone). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

[00214] In some embodiments, Compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, can be effective in the treatment of steroid resistant asthma.

[00215] In one embodiment, the regression of asthma is a decrease (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% decrease) in the level of maximal decrease from pre-allergen challenge in FEVi following allergen challenge. The level of maximal decrease from pre-allergen challenge in FEVi following allergen challenge can be measured in EAR or LAR.

[00216] In one embodiment, the regression of asthma is a decrease (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% decrease) in area under the curve (AUC) of FEVi following allergen challenge.

[00217] In one embodiment, the regression of asthma is an increase (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% increase) in the amount of methacholine that is required to induce a 20% fall in FEVi (PC20) following allergen challenge.
In one embodiment, the regression of asthma is a decrease (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% decrease) in exhaled nitric oxide level of the subject.

In one embodiment, the regression of asthma is a decrease (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% decrease) in the C-reactive protein (CRP) level of the subject.

In one embodiment, the regression of asthma is a decrease (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% decrease) in white blood cell count and/or differential cell count in induced sputum of the subject after allergen challenge.

COMBINATION THERAPY

In some embodiments, the compound provided herein is administered in combination with one or more other therapies. Such therapies include therapeutic agents as well as other medical interventions, behavioral therapies (e.g., avoidance of sunlight), and the like.

By "in combination with," it is not intended to imply that the other therapy and the compound provided herein must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the invention. The compound provided herein can be administered concurrently with, prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks before), or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks after), one or more other therapies (e.g., one or more other additional agents). In general, each therapeutic agent will be administered at a dose and/or on a time schedule determined for that particular agent. The other therapeutic agent can be administered with the compound provided herein in a single composition or separately in a different composition. Triple therapy is also contemplated herein.

In general, it is expected that additional therapeutic agents employed in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

In some embodiments, the compound provided herein is a first line treatment for a pulmonary or respiratory disease, i.e., it is used in a subject who has not been previously administered another drug intended to treat a pulmonary or respiratory disease, or one or more symptoms of the disease.

In other embodiments, the compound provided herein is a second line treatment for a pulmonary or respiratory disease, i.e., it is used in a subject who has been previously administered another drug intended to treat a pulmonary or respiratory disease, or one or more symptoms of the disease.

In other embodiments, the compound provided herein is a third or fourth line treatment for a pulmonary or respiratory disease, i.e., it is used in a subject who has been previously administered two or three other drugs intended to treat a pulmonary or respiratory disease, or one or more symptoms of the disease.
In embodiments where two agents are administered, the agents can be administered in any order. For example, the two agents can be administered concurrently (i.e., essentially at the same time, or within the same treatment) or sequentially (i.e., one immediately following the other, or alternatively, with a gap in between administration of the two). In some embodiments, the compound provided herein is administered sequentially (i.e., after the first therapeutic).

In some embodiments, the compound provided herein and the second agent are administered as separate compositions, e.g., pharmaceutical compositions. In some embodiments, the compound provided herein and the agent are administered separately, but via the same route (e.g., both by inhalation). In other embodiments, the compound provided herein and the agent are administered in the same composition, e.g., pharmaceutical composition.

In some embodiments, the compound provided herein (e.g., PBKδ inhibitor) is administered in combination with an agent that inhibits IgE production or activity. In some embodiments, the compound provided herein (e.g., PI3K8 inhibitor) is administered in combination with an inhibitor of mTOR. Agents that inhibit IgE production are known in the art and they include but are not limited to one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphthoxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (i.e., rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

In certain embodiments, wherein inflammation (e.g., COPD, asthma) is treated, prevented and/or managed, a compound provided herein can be combined with, for example: PI3K inhibitors such as GS-1 101, XL 499, GDC-0941, and AMG-3 19; BTK inhibitors such as ibrutinib and AVL-292; JAK inhibitors such as tofacitinib, fostamatinib, and GLPG0636.

In some embodiments, a compound provided herein can be combined with other agents that act to relieve the symptoms of inflammatory conditions, such as COPD, asthma, and the other diseases described herein. These agents include, but are not limited to, non-steroidal anti-inflammatory drugs (NSAIDs), e.g., acetylsalicylic acid; ibuprofen; naproxen; indomethacin; nabumetone; and tolmetin. In some embodiments, corticosteroids are used to reduce inflammation and suppress activity of the immune system.

In some embodiments, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in combination with an agent for pulmonary or respiratory diseases. Examples of agents for pulmonary or respiratory diseases include, but are not limited to, Abraxane (paclitaxel protein-bound particles for injectable suspension), Adempas (riociguat), Anoro Ellipta (umeclidinium and vilanterol inhalation powder), Breo Ellipta (fluticasone furoate and vilanterol inhalation powder), Opsumit (macitentan), Qnasl (beclomethasone dipropionate) nasal aerosol, Sirturo (bedaquiline), Dymista (azelastine hydrochloride and fluticasone propionate), Kalydeco (ivacaftor), Qnasl (beclomethasone dipropionate) nasal aerosol, Rayos (prednisone) delayed-release tablets, Surfaxin (lucinactant), Tudorza Pressair (aclidinium bromide inhalation powder), Arcapta (indacaterol...
maleate inhalation powder), Daliresp (roflumilast), Xalkori (crizotinib), Cayston (aztreonam for inhalation solution), Dulera (mometasone furoate + formoterol fumarate dihydrate), Teflaro (ceftaroline fosamil), Adcirca (tadalafil), Tyvaso (treprostinil), Alvesco (ciclesonide), Patanase (olopatadine hydrochloride), Letairis (ambrisentan), Xyzal (levocetirizine dihydrochloride), Brovana (arformoterol tartrate), Tygacil (tigecycline), Ketek (telithromycin), Spiriva HandiHaler (tiotropium bromide), Aldurazyme (laronidase), Iressa (gefitinib), Xolair (omalizumab), Zemaïra (alpha-l-proteinase inhibitor), Clarinex, Qvar (beclomethasone dipropionate), Remodulin (treprostinil), Xopenex (levosalbuterol), Avelox I.V. (moxifloxacin hydrochloride), DuoNeb (albuterol sulfate and ipratropium bromide), Foradil Aerolizer (formoterol fumarate inhalation powder), Invanz, NasalCrom Nasal Spray, Tavist (clemastine fumarate), Tracleer (bosentan), Ventolin HFA (albuterol sulfate inhalation aerosol), Biaxin XL (clarithromycin extended-release tablets), Cefzolin and Dextrose USP, Tri-Nasal Spray (triamcinolone acetonide spray), Accolate (zafirlukast), Cacfit Injection, Proventil HFA Inhalation Aerosol, Rhinocort Aqua Nasal Spray, Tequin, Tikosyn Capsules, Allegra-D, Clemastine fumarate syrup, Curosurf, Dynabac, Infasurf, Priftin, Pulmozyme (dornase alfa), Sclerosol Intrapleural Aerosol, Singulair (montelukast sodium), Synagis, Ceftin (cefuroxime axetil), Cipro (ciprofloxacin HCl), Claritin RediTabs (10 mg loratadine rapidly-disintegrating tablet), Flonase Nasal Spray, Flovent Rotadisk, Metaproterol Sulfate Inhalation Solution (5%), Nasacort AQ (triamcinolone acetonide) Nasal Spray, Omnicef, Raxar (grepafloxacin), Serevent, Tilade (nedocromil sodium), Tobi, Vanceril 84 meg Double Strength (beclomethasone dipropionate, 84 meg) Inhalation Aerosol, Zagan (sparfloxacin) tablets, Zyflo (Zileuton), Allegra (fexofenadine hydrochloride), Astelin nasal spray, Atrovent (ipratropium bromide), Augmentin (amoxicillin/clavulanate), Azmacort (triamcinolone acetonide) Inhalation Aerosol, Breathe Right, Claritin Syrup (loratadine), Claritin-D 24 Hour Extended Release Tablets (10 mg loratadine, 240 mg pseudoephedrine sulfate), Covera-HS (verapamil), OcuHist, RespiGam (Respiratory Syncitial Virus Immune Globulin Intravenous), Tripedia (Diptheria and Tetanus Toxoids and Acellular Pertussis Vaccine Absorbed), Vancenase AQ 84 meg Double Strength, Visipaque (iodixanol), Zosyn (sterile piperacillin sodium/tazobactam sodium), Cedax (ceftibuten), and Zyrtec (cetirizine HCl).

In one embodiment, the agent for pulmonary or respiratory diseases is Arcapta (indacaterol maleate inhalation powder), Daliresp (roflumilast), Dulera (mometasone furoate + formoterol fumarate dihydrate), Alvesco (ciclesonide), Brovana (arformoterol tartrate), Spiriva HandiHaler (tiotropium bromide), Xolair (omalizumab), Qvar (beclomethasone dipropionate), Xopenex (levosalbuterol), DuoNeb (albuterol sulfate and ipratropium bromide), Foradil Aerolizer (formoterol fumarate inhalation powder), Accolate (zafirlukast), Singulair (montelukast sodium), Flovent Rotadisk (fluticasone propionate inhalation powder), Tilade (nedocromil sodium), Vanceril (beclomethasone dipropionate, 84 meg), Zyflo (Zileuton), and Azmacort (triamcinolone acetonide) Inhalation Aerosol. In one embodiment, the agent for pulmonary or respiratory diseases is Spiriva HandiHaler (tiotropium bromide).

[00233] In one embodiment, the additional therapeutic agent is selected from one or more of Advair (fluticasone and salmeterol), Breo Ellipta (fluticasone furoate and vilanterol inhalation powder), Dulera (mometasone furoate and formoterol fumarate), and Symbicort (budesonide and formoterol).
In one embodiment, the additional therapeutic agent is a corticosteroid. In one embodiment, the corticosteroid is selected from fluticasone, mometasone, and budesonide. In another embodiment, the corticosteroid is dexamethasone.

In one embodiment, the additional therapeutic agent is administered simultaneously with the compound. In another embodiment, the additional therapeutic agent is administered sequentially with the compound. In one embodiment, a pharmaceutical composition comprising the compound of formula (I) and an additional therapeutic agent is administered.

Examples of agents for pulmonary or respiratory diseases include, but are not limited to, acetylcysteine (mucomyst) selected from Tudorza Pressair (acldinium bromide), Atrovent (ipratropium), and Spiriva (tiotropium).

Examples of agents for pulmonary or respiratory diseases include, but are not limited to, beta2 agonists selected from short-acting beta2 agonists and long acting beta2 agonists. Short acting beta2 agonists include, but are not limited to, Proventil (albuterol), Tornalate (bitolterol), Xopenex (levalbuterol), Maxair (pirbuterol), and Alupent (metaproterenol). Long acting beta2 agonists include, but are not limited to, Brovana (arformoterol tartrate), Foradil (formoterol), Arcapta Neohaler (indacaterol maleate), and Serevent (salmeterol).

Examples of agents for pulmonary or respiratory diseases include, but are not limited to, combination of two agents. In one embodiment, the combination is administered through inhalation. The combination of two agents includes, but is not limited to a beta2 agonist and an anticholinergic selected from Combivent (albuterol and ipratropium) and Anoro Ellipta (umeclidinium and vilanterol inhalation powder). The combination of two agents include, but are not limited to a beta2 agonist and a corticosteroid selected from Advair (fluticasone and salmeterol), Breo Ellipta (fluticasone furoate and vilanterol inhalation powder), Dulera (mometasone furoate and formoterol fumarate), and Symbicort (budesonide and formoterol).

Examples of agents for pulmonary or respiratory diseases include, but are not limited to, corticosteroids selected from Vanceril Beclovent (beclomethasone), Pulmicort (budesonide), Alvesco (ciclesonide), Aerobid (flunisolide), Flovent (fluticasone), Asmanex (mometasone furoate), and Azmacort (triamcinolone).

Examples of agents for pulmonary or respiratory diseases include, but are not limited to, leukotriene inhibitors selected from Singular (montelukast), Accolate (zafirlukast), and Zyflo (zileuton).

Examples of agents for pulmonary or respiratory diseases include, but are not limited to, mast cell stabilizers selected from Intal (cromolyn sodium) and Tilade (nedocromil).

Examples of agents for pulmonary or respiratory diseases include, but are not limited to, phosphodiesterase 4 (PDE4) inhibitors selected from Daliresp (roflumilast).

In some embodiments, a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmacologically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in combination with an agent for immunology or infectious diseases. Examples of agents for immunology or infectious diseases include, but are not limited to, Kineret (anakinra), Lovenox (enoxaparin sodium) Injection, Makena (hydroxyprogesterone caproate injection), Myalept (metreleptin for injection), Qnasl
(beclomethasone dipropionate) nasal aerosol, Simponi (golimumab), Sitavig (acyclovir) buccal tablets, Tecfidera (dimethyl fumarate), Tivicay (dolutegravir), VariZIG, Varicella Zoster Immune Globulin (Human), Flublok (seasonal influenza vaccine), Flucelvax (influenza virus vaccine), Fulyzaq (crofelemeter), Horizant (gabapentin enacarbil), Qnasl (beclomethasone dipropionate) nasal aerosol, Rayos (prednisone) delayed-release tablets, Strimbil (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate), Tudorza Pressair (aclidinium bromide inhalation powder), Arcapta (indacaterol maleate inhalation powder), Benlysta (belimumab), Complera (emtricitabine/ritonavir/tenofovir disoproxil fumarate), Daliresp (roflumilast), Dificid (fidaxomicin), Edurant (ritonavir), Pirazyr (icatibitant), Gralise (gabapentin), Incivek (telaprevir), Nulojix (belatacept), Virectelis (boceprevir), Cayston (aztreonam for inhalation solution), Egrifta (tesamorelin for injection), Menvio (meningitis vaccine), Oravig (miconazole), Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine), Teflaro (ceftaroline fosamil), Zortress (everolimus), Zymaxid (gatifloxacin ophthalmic solution), Bepreve (bepotastine besilate ophthalmic solution), Berinert (CI Esterase Inhibitor (Human)), Besivance (besifloxacin ophthalmic suspension), Cervarix [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant], Coartem (artemether/lumefantrine), Hiberix (Haemophilus b Conjugate Vaccine; Tetanus Toxoid Conjugate), Ilaris (canakinumab), Ixiaro (Japanese Encephalitis Vaccine, Inactivated, Adsorbed), Kalbitor (ecallantide), Qutenza (capsaicin), Vibrativ (telavancin), Zirgan (ganciclovir ophthalmic gel), Aptivus (tipranavir), Astepr (azelastine hydrochloride nasal spray), Cinryze (CI Inhibitor (Human)), Intelsey (etavirine), Oxotag (amoxicillin), Rotarix (Rotavirus Vaccine, Live, Oral), Tysabri (natalizumab), Viread (tenofovir disoproxil fumarate), Altabax (retapamulin), AzaSite (azithromycin), Doribax (doripenem), Extina (ketoconazole), Isentress (raltegravir), Selzentry (maraviroc), Veramyst (fluocytosine furoate), Xyzal (levocetirizine dihydrochloride), Eraxis (anidulafungin), Gardasil (quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine), Noxafil (posaconazole), Prezista (darunavir), Rotateq (rotavirus vaccine, live oral pentavalent), Tyzeka (telbivudine), Veregen (kunecatechins), Baraduce (entecavir), Tygacil (tigecycline), Ketek (telithromycin), Tindamax, tinidazole, Xifaxan (rifaximin), Amevive (alefacept), FluMist (Influenza Virus Vaccine), Fuzeon (enfuvirtide), Lexiva (fosamprenavir calcium), Reyataz (atazanavir sulfate), Alinia (nitazoxanide), Clarinex, Daptacel, Fluzone Preservative-free, Hepsera (adefovir dipivoxil), Pediarix Vaccine, Pegasys (peginterferon alfa-2a), Restasis (cyclosporine ophthalmic emulsion), Sustiva, Vfend (voriconazole), Avelox I.V. (moxifloxacin hydrochloride), Cancidas, Peg-Intron (peginterferon alfa-2b), Rebetol (ribavirin), Spectracef, Twinrix, Valcyte (valganciclovir HC1), Xigris (drotrecogin alfa [activated]), ABREVA (docosanol), Biaxin XL (clarithromycin extended-release tablets), Cefzolin and Dextrose USP, Children’s Motrin Cold, Evoxac, Kaletra Capsules and Oral Solution, Lamisil (terbinafine hydrochloride) Solution (1%), Lotrisone (clotrimazole/betamethasone dipropionate) lotion, Malarone (atovaquone; proguanil hydrochloride) Tablet, Rapamune (sirolimus) Tablets, Rid Mousse, Tri-Nasal Spray (triamcinolone acetonide spray), Trivagizole 3 (clotrimazole) Vaginal Cream, Trizivir (abacavir sulfate; lamivudine; zidovudine AZT) Tablet, Agenerase (amprenavir), Cleocin (clindamycin phosphate), Famvir (famciclovir), Norvir (ritonavir), Panretin Gel, Rapamune (sirolimus) oral solution, Relenza, Synercid I.V., Tamiflu capsule, Vistide
(cidofovir), Allegra-D, CellCept, Clemastine fumarate syrup, Dynabac, REBETRON (TM) Combination Therapy, Simulect, Timentin, Viroptic, INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), Acyclovir Capsules, Aldara (imiquimod), Aphthasol, Combivir, Condyllox Gel 0.5% (pokofiloxy), Flagyl ER, Flonase Nasal Spray, Fortovase, INFERGEN (interferon alfacon-1), Intron A (interferon alfa-2b, recombinant), Norvir (ritonavir), Rescriptor (delavirdine mesylate tablets), SPORANOX (itraconazole), Stromectol (ivermectin), Taxol, Trovan, VIRACEPT (nelfinavir mesylate), Zerit (stavudine), Albenza (albendazole), Aphthasol (Amlexanox), Carrington patch, Confide, Crixivan (Indinavir sulfate), Gastrocrom Oral Concentrate (cromolyn sodium), Havrix, Lamisil (terbinafine hydrochloride) Tablets, Leukine (sargramostim), Oral Cytovene, RespiGam (Respiratory Syncitial Virus Immune Globulin Intravenous), Videx (didanosine), Viramune (nevirapine), Vitrasert Implant, Zithromax (azithromycin), Cedax (ceftibuten), Clarithromycin (Biaxin), Epivir (lamivudine), Invirase (saquinavir), Valtrex (valacyclovir HCl), and Zyrtec (cetirizine HCl).

KITS

[00244] Kits are also provided herein. The kits include a compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a composition thereof, in suitable packaging, and written material. The written material can include any of the following information: instructions for use, discussion of clinical studies, listing of side effects, scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like. The written material can indicate or establish the activities and/or advantages of the composition, and/or describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider.

Such information can be based on the results of various studies, for example, studies using experimental animals involving in vivo models and/or studies based on human clinical trials. In some embodiments, the kit contains a device for inhalation. The kit can further contain another therapy (e.g., another agent) and/or written material such as that described above that serves to provide information regarding the other therapy (e.g., the other agent). In some embodiments, the compound provided herein (e.g., Compound 1), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, and the agent are provided as separate compositions in separate containers within the kit. In some embodiments, the compound of the present invention and the agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (e.g., inhalable formulation in discreet container, foil wrapping to minimize exposure to air, and the like) are known in the art and can be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits can also, in some embodiments, be marketed directly to the consumer.
EXAMPLES

Example 1: Pharmacokinetics and Reduction of LPS-Induced Neutrophilia

\[00245\] Compound 1 was administered intratracheally (i.t.) to rats at an amount of 1 µg/kg, 10 µg/kg or 100 µg/kg. In addition, the following administrations were performed as controls: (1) oral (p.o.) administration of Compound 1 at 10 mg/kg (free base form of Compound 1); (2) intratracheal administration of saline (vehicle) at 0.25 mL/rat; (3) intratracheal administration of LPS (vehicle) at 1 µg LPS/rat; and (4) intratracheal administration of budesonide at 0.3 mg/kg, which is a positive control. At one hour post-administration, neutrophilia was induced in the lung by treatment with LPS, and the samples were collected by bronchoalveolar lavage (BAL) at varying hours post-administration and subjected to further examination.

\[00246\] In the first set of examination, the levels of Compound 1 in lung, bronchoalveolar lavage fluid (BALF), and plasma were determined, and the results are shown below in Tables 1 and 2.

**Table 1: Levels in Lung and BALF**

<table>
<thead>
<tr>
<th>Dose(^a)</th>
<th>Route</th>
<th>Timepoint (hr)</th>
<th>Mean Compound 1 Level/Concentration</th>
<th>% in Lung(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (nM)</td>
<td>Lung (nmol)</td>
<td>BALF (nM)</td>
<td>BALF (nmol)</td>
<td></td>
</tr>
<tr>
<td>1 µg/kg</td>
<td>i.t.</td>
<td>5.5</td>
<td>478</td>
<td>0.73</td>
</tr>
<tr>
<td>10 µg/kg</td>
<td>i.t.</td>
<td>5.5</td>
<td>5432</td>
<td>8.05</td>
</tr>
<tr>
<td>100 µg/kg</td>
<td>i.t.</td>
<td>5.5</td>
<td>55432</td>
<td>86.66</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>p.o.</td>
<td>5.5</td>
<td>7790</td>
<td>11.28</td>
</tr>
</tbody>
</table>

**Table 2: Levels in Plasma**

<table>
<thead>
<tr>
<th>Dose(^a)</th>
<th>Route</th>
<th>Timepoint (hr)</th>
<th>Mean Plasma Conc (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 µg/kg</td>
<td>i.t.</td>
<td>1.5</td>
<td>BLQ</td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>5.5</td>
<td>BLQ</td>
</tr>
<tr>
<td>10 µg/kg</td>
<td>i.t.</td>
<td>1.5</td>
<td>2.23</td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>5.5</td>
<td>1.60</td>
</tr>
<tr>
<td>100 µg/kg</td>
<td>i.t.</td>
<td>1.5</td>
<td>22.2</td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>5.5</td>
<td>10.7</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>p.o.</td>
<td>1.5</td>
<td>686</td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>5.5</td>
<td>963</td>
</tr>
</tbody>
</table>

\(^a\) Vehicle = Symbiveh® pH=5.0; \(^b\) Relative to dose

BLQ: below limit of quantitation

\[00247\] As shown in the above Tables, the majority of Compound 1 was found in lung tissue following intratracheal administration at all doses tested, while very low levels of Compound 1 were detected in BALF and
plasma. Approximately 100% of the i.t. dose was found to reach the lung tissue under the conditions described above. It was also found that, an oral administration at 10 mg/kg provides a comparable level of Compound 1 in the lung tissue provided by intratracheal administration at 10 µg/kg dose, and the oral administration resulted in significantly higher levels of Compound 1 in BALF than those provided by the intratracheal administration.

Furthermore, it was also found that intratracheal administration of Compound 1 results in prolonged retention of Compound 1 in the lung tissue, i.e., about 40% of the initial dose remained in lung homogenates 24 hours after administration (Data not shown).

[00248] In the second set of examination, the effect of Compound 1 on reducing LPS induced neutrophilia was assessed. As shown in FIG. 1A and FIG. 1B, it was found that Compound 1 given orally at 10 mg/kg was equivalent to budesonide. In addition, the lowest administered dose by the intratracheal route (1 µg/kg) was shown to be still above the likely ED50 in this assay, evidencing that intratracheal administration results in efficacy.

Example 2: Studies with Smoking Mouse Model of Chronic Obstructive Pulmonary Disease (COPD)

[00249] Studies of the effect of the compounds provided herein on the smoking mouse model of COPD can be conducted using methods known in the art. Provided below is an illustrative example of such method. The mice are exposed to cigarette smoke for 4 days in a whole body exposure box. Whole body exposure is conducted for a certain amount of time in a custom made cylindrical 32 L Perspex box (e.g., Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany) before each cigarette smoke exposure or before lung function measurement. Animals are separated by stainless steel spacers. The floor of the box is additionally heated (e.g., 38 °C) to maintain the physiological body temperature of the animals. Control animals receive solvent as placebo. On days one and two, mice are exposed to the mainstream smoke of cigarettes. Exposure to the smoke of each cigarette lasts for about 15 min followed by an 8 min exposure with fresh room air. Every second cigarette an additional break of 24 min with exposure to fresh room air is conducted. A semi-automatic cigarette lighter and smoke generator with an electronic timer is used to control the cigarette exposure (e.g., Boehringer Ingelheim Pharma GmbH&Co. KG, Biberach, Germany). Cigarette smoke particle concentration is monitored by a real time ambient particle monitor (e.g., MicroDustPro, Casella, Amherst, NH, USA). Control animals are exposed to room air. See e.g., L. Wollin, et al., Pulmonary Pharmacology & Therapeutics 23 (2010) 345-354.

[00250] Compounds provided herein can be administered orally or intratracheally (i.t.) using methods known in the art. For example, a compound provided herein can be administered orally as a solid or a solution. Alternatively, a compound provided herein can be administered intratracheally by aerosolizing a solution of the compound with a jet nebulizer. A compound provided herein can be administered at various concentration and schedules. For example, whole body exposure of a compound provided herein can be administered for 5 min and 1 h prior to exposure to cigarette smoke.

[00251] Differential cell counts can be determined in the bronchoalveolar lavage fluid (BALF). For example, the total BALF cell counts and the amount of neutrophils in the samples can be used to evaluate the efficacy of a
compound provided herein. Models of cigarette-smoke induced pulmonary inflammation have an increased BALF total cell count and also the amount of neutrophils. As such, a decrease of BALF total cell count and the amount of neutrophil in models administered with a compound provided herein as compared to a control model (without administration of a compound provided herein) can illustrate the effectiveness of a compound provided herein in the treatment of pulmonary inflammation. See e.g., L. Wollin, et al., Pulmonary Pharmacology & Therapeutics 23 (2010) 345-354.

Further, lung sections stained with e.g., H&E or AB/PAS of the control models (e.g., models without administration of a compound provided herein) can be compared with lung sections of models administered with a compound provided herein. H&E staining can show inflammation and alveolar infiltrates in the lungs. AB/PAS staining can show the mucus content in the goblet cells of the large airway. See e.g., L. Wollin, et al., Pulmonary Pharmacology & Therapeutics 23 (2010) 345-354.

Example 3: Lung inflammation assay

Compounds provided herein can be tested using one or both of the LPS-induced lung inflammation assay and the ovalbumin-induced lung inflammation assay.

To perform the LPS-induced lung inflammation assay, compounds are dosed orally. A group is dosed with vehicle only and dexamethasone is used in another group as positive control. Pulmonary inflammation is determined 6 h after intranasal instillation of LPS. The following parameters can be evaluated: total number of leukocytes and number of neutrophils in bronchoalveolar lavage fluid (BALF).

In the ovalbumin-induced lung inflammation assay, compounds are dosed orally. A group is dosed with vehicle only and dexamethasone is used in another group as positive control. Pulmonary inflammation is determined 4 days after 4 consecutive daily intranasal instillation of ovalbumin. Compounds are given by gavage 30 min before each challenge (4 challenges) at the indicated doses. The following parameters can be evaluated: total number of leukocytes and number of eosinophils in BALF.

Compounds provided herein can also be administered intratracheally or by inhalation.

Example 4: Smoke-induced steroid resistant inflammation with and without dexamethasone

The purpose of this study is to determine whether treatment with a compound provided herein (e.g., Compound 1) can prevent the steroid resistant pulmonary inflammation induced by exposing mice for 10 days to cigarette smoke. Mice are first exposed for 5 days to cigarette smoke to induce glucocorticosteroid resistance. Thereafter, the animals are exposed for an additional 5 days to cigarette smoke together with the administration of a compound provided herein (e.g., Compound 1) to investigate whether the glucocorticosteroid resistance can be diminished.
Balb/c byJ mice (weight 24-26 gr; 10-12 weeks old) are exposed to standard air or cigarette smoke for 10 days ("whole body exposure"). Mice are exposed when they are sitting together in one Perspex box. The cigarettes that are used are special research cigarettes (standardized from Kentucky University: 3R4F) without filter.

Dose and time of exposure are increasing dose and time starting at the 1st until the 10th day of exposure (twice a day (= 2 runs); interval exposure is 5 hours):

1st day: run 1 = 2 pairs of cigarettes and run 2 = 3 pairs of cigarettes. The smoke exposure dose and time = 10 -15 min. (CO dose = 150-300 ppm; 0 2 concentration = 20.8 % measured by Baccharach PCA3-analyzer);

2nd day: run 1 = 4 pairs of cigarettes and run 2 = 5 pairs of cigarettes. The smoke exposure dose and time = 20-25 min. (CO dose = 150-300 ppm; 0 2 concentration = 20.8 %);

3rd day: run 1 = 6 pairs of cigarettes and run 2 = 7 pairs of cigarettes. The smoke exposure dose and time = 0-35 min. (CO dose = 150-300 ppm; 0 2 concentration = 20.8 %);

4th day till the 10th day: run 1 = 7 pairs of cigarettes and run 2 = 7 pairs of cigarettes. The smoke exposure dose and time = 35 min. (CO dose = 150-300 ppm; 0 2 concentration = 20.8 %).

Animals are treated with a compound provided herein (e.g., Compound 1), or Vehicle solution 1 or 2 e.g., orally or intratracheally daily from days 6 until 10. Dexamethasone (5 mg/kg) is administered daily intraperitoneally (IP) from days 6 until 10.

Body weight of the individual animals is monitored daily from day 1 until day 11. Mice are sacrificed 1 day after the last exposure to air or CS (day 10). Blood is collected via a heart puncture and the isolated serum is collected and stored at -30°C. Lungs are lavaged; BALF cells are isolated counted and differentiated. BAL fluid is stored for determination of cytokines/chemokines.

Example 5: Rat ovalbumin-induced asthma model

The purpose of this study was to evaluate the effect of a compound provided herein in the rat ovalbumin-induced asthma model. All animals were sensitized by intraperitoneal (IP) injection of ovalbumin (2 mg/mL) and aluminum hydroxide (10 mg/mL) on Days 1, 2, and 3. On Day 21 animals in Group 1 were dosed with the Reference Item (5% NMP, 10% Solutol HS-15, 85% PEG 400), Groups 2 to 5 were administered Compound 1 (e.g., free base form) by oral gavage, and Group 6 received an IP injection of dexamethasone. One hour following dose administration, animals were placed in whole body chambers and challenged with 1% ovalbumin. At 48 hours following ovalbumin challenge, animals were euthanized and bronchoalveolar lavage fluid (BALF) was collected and assessed for total and differential cell counts.

The study design is detailed in the table below:

<table>
<thead>
<tr>
<th>Group/ Identification</th>
<th>IP Sensitization</th>
<th>Dose Level a</th>
<th>Dose Volume b</th>
<th>Dose Concentration b</th>
<th>Nebulized Challenge c</th>
<th>BALF/Lung Collection Time d</th>
<th>TK Animals e</th>
<th>No. of Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Reference Item (Control)</td>
<td>+</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>+</td>
<td>48</td>
<td>+</td>
<td>13</td>
</tr>
</tbody>
</table>
Animals were administered Reference Item (Gr. 1), Compound 1 (Gr. 2 to 5) or dexamethasone the 1% OVA in saline challenge on Day 21. All animals were challenged with a nebulized aerosol of 1% OVA in saline on Day 21. BALF in 7 animals/group or Lung in 3 animals/group were collected 48 hours post Day 21 challenge. TK collection from Group 1 (3 animals) at two timepoints (2 timepoints/animal) and from Groups 2 to 5 (6 animals/group) at six timepoints (up to 3 timepoints/animal).

[00264] FIG. 2A shows that Compound 1 is active in rat ovalbumin-induced asthma model as measured by white blood cell counts. FIG. 2B shows that Compound 1 is active in rat ovalbumin-induced asthma model as measured by eosinophils.

[00265] Compounds provided herein can also be administered intratracheally or by inhalation in this study.

Example 6: Pharmacokinetics

[00266] The purpose of the study was to evaluate the pharmacokinetics of Compound 1 rats, dogs, and monkeys. The study design is detailed in the table below:

<table>
<thead>
<tr>
<th>Species</th>
<th>Dosing group</th>
<th>Route</th>
<th>Feeding Status</th>
<th>N and Gender</th>
<th>Dose Level (mg/kg)</th>
<th>Dose Conc. (mg/mL)</th>
<th>Dose Volume (mL/kg)</th>
<th>Blood Sample Collection Time Points (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>1</td>
<td>PO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>fed</td>
<td>3M, 3F</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>pre-dose, 0.25, 0.5, 1, 2, 4, 6, 24 h</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>IV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>fed</td>
<td>3M, 3F</td>
<td>2</td>
<td>0.8</td>
<td>2.5</td>
<td>Pre-dose, 0.083, 0.25, 0.5, 1, 2, 4, 6, 24 h</td>
</tr>
<tr>
<td>Dog</td>
<td>1</td>
<td>PO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>fasted</td>
<td>2M, 2F</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>Pre-dose, 0.25, 0.5, 1, 2, 4, 8,12, 24</td>
</tr>
</tbody>
</table>

<sup>a</sup> All animals were sensitized with a 1 mL IP injection of OVA on Days 1, 2 and 3.

<sup>b</sup> Animals were administered Reference Item (Gr. 1), Compound 1 (Gr. 2 to 5) or dexamethasone (Gr. 6), 1 hour prior to the 1% OVA in saline challenge on Day 21.

<sup>c</sup> All animals were challenged with a nebulized aerosol of 1% OVA in saline on Day 21.

<sup>d</sup> BALF in 7 animals/group or Lung in 3 animals/group were collected 48 hours post Day 21 challenge.

<sup>e</sup> TK collection from Group 1 (3 animals) at two timepoints (2 timepoints/animal) and from Groups 2 to 5 (6 animals/group) at six timepoints (up to 3 timepoints/animal).
Below is a table that details the results of the pharmacokinetics of compound 1 in rats, dogs and monkeys:

<table>
<thead>
<tr>
<th>Oral Absorption</th>
<th>Bioavailability (%)</th>
<th>Rat = 50%</th>
<th>Dog = 73%</th>
<th>Monkey = 87%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)*</td>
<td></td>
<td>Rat = 836</td>
<td>Dog = 1995</td>
<td>Monkey = 2058</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td></td>
<td>Rat = 2.3h</td>
<td>Dog = 1.9h</td>
<td>Monkey = 2.5h</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td></td>
<td>Rat = 3.7</td>
<td>Dog = 7.2</td>
<td>Monkey = 4.4</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-last&lt;/sub&gt; (ng<em>h/mL)</em></td>
<td></td>
<td>Rat = 8734</td>
<td>Dog = 15584</td>
<td>Monkey = 12190</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Volume of distribution (L)</th>
<th>Rat = 2.1</th>
<th>Dog = 2.5</th>
<th>Monkey = 1.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary pathways in-vitro and in-vivo (non-clinical species)</td>
<td>Phase I (oxidation)*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Metabolism phenotyping</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/h/kg)</td>
<td></td>
<td>Rat = 0.69</td>
</tr>
</tbody>
</table>

| Elimination | CYP Inhibition | Reversible inhibition >10 μM (all CYPs) No time-dependent inhibition observed |
The results show that Compound 1 has good oral bioavailability in rat, dog and monkey. Compound 1 achieves high plasma concentrations rapidly. Compound 1 has good systemic exposure (area under the concentration time curve AUC) in non-clinical species. Compound 1 also exhibits dose-exposure proportionality.

The volume of distribution of Compound 1 shows that it has potential to have good tissue distribution. The Compound 1 metabolism profile in non-clinical species is consistent with human. Primary metabolic pathway(s). Compound 1 metabolism is expected to be primarily CYP3A4 mediated. Compound 1 has a low clearance in rat, dog and monkey. Compound 1 is not considered a reversible or time-dependent inhibitor of CYP450 and has the potential to induce CYP450 expression. Compound 1 is a weak substrate of P-gp and is therefore not expected to pass the blood brain barrier (i.e. not expected to enter the brain).

**Example 7: Whole blood assays**

Monocyte Activation Assay

Evaluation of monocyte activation was performed by measuring pAKT after cell stimulation. Whole blood was pre-treated with Compound 1 for 30 minutes. Cells were stimulated with LPS (PI3K-8) or fMLP (PI3K-γ). The number of pAKT positive CD14 positive monocytes in compound-treated blood compared to the untreated control was used to determine the percent inhibition by compound concentration. Data were plotted using Prism software and IC\textsubscript{50} values were determined.

Compound 1 is active in PI3K-delta and PI3K-gamma dependent whole blood assays. The table below details the results from a delta assay. The values represent the IC50s.

<table>
<thead>
<tr>
<th></th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
<th>Average</th>
<th>Std Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT (nM)</td>
<td>61.5</td>
<td>125.5</td>
<td>69.6</td>
<td>85.5</td>
<td>34.8</td>
</tr>
<tr>
<td>Monocyte (nM)</td>
<td>35.7</td>
<td>238.9</td>
<td>123.6</td>
<td>132.7</td>
<td>101.9</td>
</tr>
</tbody>
</table>

The table below details the results from a gamma assay. The values represent the IC50s.

<table>
<thead>
<tr>
<th></th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
<th>Average</th>
<th>Std Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT (nM)</td>
<td>858.2</td>
<td>2278</td>
<td>1298</td>
<td>1478.1</td>
<td>726.8</td>
</tr>
<tr>
<td>Monocyte (nM)</td>
<td>591.7</td>
<td>451.2</td>
<td>276.1</td>
<td>439.7</td>
<td>158.1</td>
</tr>
</tbody>
</table>

Primary Human B and T-cell Proliferation Assays

[00271] Human peripheral blood CD 19+ B-cells were purchased from Allcells (Emeryville, CA). Pre-diluted compound in DMSO or DMSO alone (control) were incubated with cells (100,000 cells in RPMI-1640 medium supplemented with 10% fetal calf serum, penicillin, streptomycin and 50 µM β-mercaptoethanol) for 1 hour at 37°C (final DMSO 0.1%). For stimulation of B-cell proliferation, a cocktail consisting of goat anti-human IgM (Jackson ImmunoResearch) and mouse anti-human CD40 (BD Biosciences Pharmingen) were added yielding a final concentration of 10 µg/mL anti-IgM and 3 µg/mL anti-CD40. For stimulation of T-cell proliferation, freshly isolated human PBMCs were stimulated with ConA (Sigma Aldrich) at final concentration of 5µg/mL. Cells were incubated at 37°C with 5% CO₂ for either 7 days (PBMCs) or 4 days (B-cells) to get optimal signal to noise for each assay. Cell number was measured using the CellTiter-Glo Luminescent Cell Viability Assay reagent (Promega). The table below details the results and the values represent the IC50s.

<table>
<thead>
<tr>
<th>Donor 1 (nM)</th>
<th>Donor 2 (nM)</th>
<th>Donor 3 (nM)</th>
<th>Average (nM)</th>
<th>Std Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cell</td>
<td>0.15</td>
<td>0.25</td>
<td>0.36</td>
<td>0.25</td>
</tr>
<tr>
<td>T cell</td>
<td>9.3</td>
<td>12.2</td>
<td>10.75</td>
<td>2.1</td>
</tr>
</tbody>
</table>

T Cell Recall assay

[00272] Antigen specific T cell activation requires the activity of antigen presenting cells and antigen specific T cells. In this mouse system MOG specific T cells were generated through immunization, and specific recall was achieved by using the MOG peptide to challenge whole splenocytes, which also have cells that can serve as antigen presenting cell. Specific T cell recall were postulated to be dependent on PI3K-8 based on knock-out studies in mice, and with specific antigen activation of human cells. Compound 1 was evaluated for its ability to inhibit mouse antigen specific T cell recall.

[00273] Spleenocytes from MOG immunized mice were plated in 96-well tissue culture plates in T cell media. After a 1 hour rest period the cells were treated with Compound 1, and then activated by treatment with MOG peptide. Cytokines were measured using a custom mouse cytokine array (mouse IL-2, mouse IFN-γ, mouse IL-17a, and mouse TNF-α). Percent inhibition curves were generated and IC₅₀ values were calculated.

[00274] Compound 1 was stored as a 10 mM stock in dimethyl sulfoxide (DMSO) at room temperature. A titration of Compound 1 starting at 1000 nM and diluted serially four fold across 9 points was used to define IC₅₀ values for this compound in the mouse T cell recall assay. Compound 1 was able to inhibit IL-2, IL-17a, and IFN-γ in a dose dependent manner. A summary of IC₅₀ values is shown in the table below.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>0.62</td>
</tr>
<tr>
<td>IL-2</td>
<td>18</td>
</tr>
<tr>
<td>IL-17a</td>
<td>3.1</td>
</tr>
<tr>
<td>Compound 1 experiment 2</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Average</td>
<td>0.77</td>
</tr>
<tr>
<td>St. Dev</td>
<td>0.21</td>
</tr>
</tbody>
</table>

[00275] Compound 1 is a potent inhibitor of mouse T cell recall, inhibiting IFN-γ, IL-2, and IL-17a production with low nM potency.

[00276] While exemplary embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein can be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.
WHAT I CLAIMED IS:

1. A method of treating, preventing, and/or managing a pulmonary or respiratory disease in a subject, comprising administering to a subject in need thereof by inhalation or by intratracheal administration a therapeutically or prophylactically effective amount of a compound of formula (I):

![Chemical Structure](attachment:image)

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound.

2. A method of eliciting prolonged anti-inflammatory effect in lung in a subject suffering from a pulmonary or respiratory disease, comprising administering to the subject by inhalation or by intratracheal administration a therapeutically or prophylactically effective amount of a compound of formula (I):

![Chemical Structure](attachment:image)

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, or a pharmaceutical composition comprising the compound, wherein the compound is retained in lung for a period longer than what is provided by oral administration.

3. The method of claim 2, wherein the compound is retained in lung for about 1 hour, about 3 hours, about 6 hours, about 12 hours, about 24 hours, about 48 hours, or about 72 hours longer than what is provided by oral administration.

4. The method of any one of claims 1-3, wherein the compound is retained in lung for about 1 hour or about 3 hours.
5. The method of any one of claims 1-4, wherein the amount of the compound inhaled by the subject is less than 0.01 µg/kg, less than 0.02 µg/kg, less than 0.05 µg/kg, less than 0.1 µg/kg, less than 0.2 µg/kg, less than 0.5 µg/kg, less than 1 µg/kg, less than 2 µg/kg, less than 5 µg/kg, less than 10 µg/kg, less than 20 µg/kg, less than 50 µg/kg, or less than 100 µg/kg.

6. The method of any one of claims 1-4, wherein the amount of the compound inhaled by the subject is about 0.01 µg/kg, about 0.02 µg/kg, about 0.05 µg/kg, about 0.1 µg/kg, about 0.2 µg/kg, about 0.5 µg/kg, about 1 µg/kg, about 2 µg/kg, about 5 µg/kg, about 10 µg/kg, about 20 µg/kg, about 50 µg/kg, or about 100 µg/kg.

7. The method of any one of claims 1-4, wherein the amount of the compound inhaled by the subject is from about 0.01 µg/kg to about 100 µg/kg, from about 0.01 µg/kg to about 50 µg/kg, from about 0.01 µg/kg to about 20 µg/kg, from about 0.01 µg/kg to about 10 µg/kg, from about 0.01 µg/kg to about 5 µg/kg, from about 0.01 µg/kg to about 1 µg/kg, from about 0.05 µg/kg to about 1 µg/kg, or from about 0.1 µg/kg to about 1 µg/kg.

8. The method of any one of claims 1-4, wherein the compound is administered at a dose of less than 0.01 µg/kg/day, less than 0.02 µg/kg/day, less than 0.05 µg/kg/day, less than 0.1 µg/kg/day, less than 0.2 µg/kg/day, less than 0.5 µg/kg/day, less than 1 µg/kg/day, less than 2 µg/kg/day, less than 5 µg/kg/day, less than 10 µg/kg/day, less than 20 µg/kg/day, less than 50 µg/kg/day, or less than 100 µg/kg/day.

9. The method of any one of claims 1-4, wherein the compound is administered at a dose of about 0.01 µg/kg/day, about 0.02 µg/kg/day, about 0.05 µg/kg/day, about 0.1 µg/kg/day, about 0.2 µg/kg/day, about 0.5 µg/kg/day, about 1 µg/kg/day, about 2 µg/kg/day, about 5 µg/kg/day, about 10 µg/kg/day, about 20 µg/kg/day, about 50 µg/kg/day, or about 100 µg/kg/day.

10. The method of any one of claims 1-4, wherein the compound is administered at a dose of from about 0.01 µg/kg/day to about 100 µg/kg/day, from about 0.01 µg/kg/day to about 50 µg/kg/day, from about 0.01 µg/kg/day to about 20 µg/kg/day, from about 0.01 µg/kg/day to about 10 µg/kg/day, from about 0.01 µg/kg/day to about 5 µg/kg/day, from about 0.01 µg/kg/day to about 1 µg/kg/day, from about 0.05 µg/kg/day to about 1 µg/kg/day, or from about 0.1 µg/kg/day to about 1 µg/kg/day.

11. The method of any one of claims 1-10, wherein the compound is administered once daily (QD), twice daily (BID), three times daily (TID), or four times daily (QID).

12. The method of any one of claims 1-11, wherein administering an effective amount of the compound does not result in, or results in reduced, one or more common side effects associated with treatment of pulmonary or respiratory diseases.
13. The method of any one of claims 1-12, wherein the common side effect associated with treatment of pulmonary or respiratory diseases is poor growth, decreased bone density, disseminated varicella infection, easy bruising, cataracts, glaucoma, adrenal gland suppression, stomach upset, headache, liver test abnormalities, skin rashes, Churg Strauss syndrome, bad taste in month, cough, itching, sore throat, sneezing, stuffy nose, viral illness, upper respiratory tract infections, sinusitis, feeling dizzy or faint, hives, changes in voice, swelling of the tongue, or difficulty in swallowing.

14. The method of any one of claims 1-13, wherein administering an effective amount of the compound reduces one of more of symptoms associated with pulmonary or respiratory diseases.

15. The method of claim 14, wherein the symptom associated with pulmonary or respiratory diseases is wheezing, coughing, chest tightness, shortness of breath, difficulty in breathing, or use of accessory muscle.

16. The method of any one of claims 1-15, wherein administering an effective amount of the compound by inhalation results in higher than about 20%, higher than about 30%, higher than about 40%, or higher than about 50% of the administered dose of the compound remaining in lung of the subject at about 24 hours after the administration.

17. The method of any one of claims 1-16, wherein administering an effective amount of the compound by inhalation results in that the lung concentration of the compound is about 100, about 200, about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, or about 10000 times higher than the plasma concentration of the compound at about 5 hours after the administration.

18. The method of any one of claims 1-16, wherein administering an effective amount of the compound by inhalation results in that the lung concentration of the compound is about 100, about 200, about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, or about 10000 times higher than the plasma concentration of the compound at about 12 hours after the administration.

19. The method of any one of claims 1-16, wherein administering an effective amount of the compound by inhalation results in that the lung concentration of the compound is about 100, about 200, about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, or about 10000 times higher than the plasma concentration of the compound at about 24 hours after the administration.

20. The method of any one of claims 1-19, wherein the pulmonary or respiratory disease is selected from the group consisting of pulmonary inflammation, asthma, cystic fibrosis, emphysema, chronic obstructive pulmonary disorder (COPD), chronic bronchitis, bronchiectasis, acute respiratory distress syndrome, restrictive lung diseases, respiratory tract infections, pleural cavity diseases, pulmonary vascular disease, pulmonary embolism, pulmonary arterial hypertension, pulmonary edema, pulmonary hemorrhage, and pulmonary hyperplasia.
21. The method of claim 20, wherein the pulmonary or respiratory disease is chronic obstructive pulmonary disorder.

22. The method of claim 20, wherein the pulmonary or respiratory disease is asthma.

23. The method of claim 22, wherein the asthma is selected from the group consisting of severe or refractory asthma, atopic asthma, non-atopic asthma, type 1 brittle asthma, type 2 brittle asthma, asthma attack, status asthmaticus, exercise-induced asthma, and occupational asthma.

24. The method of any one of claims 1-23, wherein the subject has received previous treatment for a pulmonary or respiratory disease.

25. The method of claim 24, wherein the subject has demonstrated progression on the previous treatment.

26. The method of claim 24, wherein the subject has developed resistance to previous treatment.

27. The method of any one of claims 24-26, wherein the previous treatment is steroid.

28. The method of claim 27, wherein the steroid is dexamethasone.

29. The method of any one of claims 1-28, wherein the subject is a mammal.

30. The method of claim 29, wherein the subject is a human.

31. The method of any one of claims 1-30, wherein the compound is a sulfuric acid salt of the compound of formula (I).

32. The method of claim 31, wherein the compound is a bis-sulfuric acid salt, mono-sulfuric acid salt, or hemi-sulfuric acid salt of the compound of formula (I).

33. The method of claim 31, wherein the compound is a bis-hydrogensulfate salt of the compound of formula (I).

34. The method of claim 33, wherein the compound is crystalline Form 1 of the bis-hydrogensulfate salt of the compound of formula (I).

35. The method of any one of claims 1-30, wherein the compound is the free base of the compound of formula (I).
36. The method of any one of claims 1-35, further comprising administration of an additional therapeutic agent.

37. The method of claim 36, wherein the additional therapeutic agent is administered simultaneously or sequentially with the compound.

38. The method of any one of claims 1-35, wherein a pharmaceutical composition comprising the compound of formula (I) and an additional therapeutic agent is administered.

39. The method of any one of claims 36-38, wherein the additional therapeutic agent is selected from one or more of Arcapta (indacaterol maleate inhalation powder), Daliresp (roflumilast), Dulera (mometasone furoate + formoterol fumarate dihydrate), Alvesco (ciclesonide), Brovana (arformoterol tartrate), Spiriva HandiHaler (tiotropium bromide), Xolair (omalizumab), Qvar (beclomethasone dipropionate), Xopenex (levalbuterol), DuoNeb (albuterol sulfate and ipratropium bromide), Foradil Aerolizer (formoterol fumarate inhalation powder), Accolate (zafirlukast), Singular (montelukast sodium), Flovent Rotadisk (fluticasone propionate inhalation powder), Tilade (nedocromil sodium), Vanceril (beclomethasone dipropionate, 84 meg), Zyflo (Zileuton), and Azmacort (triamcinolone acetonide) Inhalation Aerosol.

40. The method of any one of claims 36-38, wherein the additional therapeutic agent is selected from one or more of Advair (fluticasone and salmeterol), Breo Ellipta (fluticasone furoate and vilanterol inhalation powder), Dulera (mometasone furoate and formoterol fumarate), and Symbicort (budesonide and formoterol).

41. The method of any one of claims 36-38, wherein the additional therapeutic agent is a corticosteroid.

42. The method of claim 41, wherein the corticosteroid is selected from fluticasone, mometasone, and budesonide.

43. The method of claim 41, wherein the corticosteroid is dexamethasone.
Effect of Compound 1 on LPS Induced Neutrophilia in BAL (4 hours duration)

FIG. 1A

FIG. 1B
**White blood cells**

- Vehicle control
- Cmpd 1 0.078 mg/kg
- Cmpd 1 0.3 mg/kg
- Cmpd 1 1.25 mg/kg
- Cmpd 1 5 mg/kg
- Dexamethasone

**FIG. 2A**

**Eosinophils**

- Vehicle control
- Cmpd 1 0.078 mg/kg
- Cmpd 1 0.3 mg/kg
- Cmpd 1 1.25 mg/kg
- Cmpd 1 5 mg/kg
- Dexamethasone

**FIG. 2B**
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/519 A61P11/00

According to International Patent Classification (IPC) onto both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered a priori invention or cannot be considered to involve an inventive step when the document is taken in combination with one or more other such documents, such combination being obvious to a person skilled in the art

“A” document member of the same patent family

Date of the actual completion of the international search: 8 July 2015

Date of mailing of the international search report: 14/07/2015

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040;
Fax: (+31-70) 340-3016

Authorized officer:
Loher, Flori an

Form PCT/ISA210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>J. DOUKAS ET AL: &quot;Aerosol ized Phosphoinos t ide 3-Ki nase / Inhibitor TG100-115 [3- [2,4-Di amino-6- (3-hydroxyphenyl )pter i di n-7-yl ] phenol ] as a Therapeutic Candidate for Asthma and Chronic Obstructive Pulmonary Disease&quot;, JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 328, no. 3, 4 December 2008 (2008-12-04), pages 758-765, XP55200684, ISSN: 0022-3565, DOI: 10.1124/jpet.108.144311 page 760, right-hand column - page 762</td>
<td>1-43</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AU 2012302197 A1</td>
<td>02-05-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2846431 A1</td>
<td>07-03-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 103998442 A</td>
<td>20-08-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2751093 A1</td>
<td>09-07-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2014525438 A</td>
<td>29-09-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20140075693 A</td>
<td>19-06-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PE 13712014 A1</td>
<td>13-10-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 201311663 A1</td>
<td>16-03-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013053362 A1</td>
<td>28-02-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014100214 A1</td>
<td>10-04-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014288048 A1</td>
<td>25-09-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2013032591 A1</td>
<td>07-03-2013</td>
</tr>
</tbody>
</table>