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Liu

(54) SUBSTITUTED ISOINDOLINE-1,3-Dione
DERIVATIVES

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ABSTRACT

This invention relates to novel substituted isoidoline-1,3-
dione derivatives and pharmaceutically acceptable salts
thereof. More specifically, the invention relates to novel sub­
dstituted isoindoline-1,3-dione derivatives that are analogs of
apremilast. This invention also provides compositions com­
prising a compound of this invention and a carrier and the use of
disclosed compounds and compositions in methods of
treating diseases and conditions that are beneficially treated
by administering apremilast.

35 Claims, No Drawings
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This invention relates to novel substituted isoindoline-1,3-dione derivatives and pharmaceutically acceptable salts thereof.
More specifically, the invention relates to novel substituted isoindoline-1,3-dione derivatives that are analogues of apremilast. This invention also provides compositions comprising a compound of this invention and a carrier and the use of disclosed compounds and compositions in methods of treating diseases and conditions that are beneficially treated by administering apremilast.

DETAILED DESCRIPTION OF THE INVENTION

The term “treat” means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

“Disease” means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of apremilast will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada E et al., Seikagaku 1994, 66:15; Gannes L Z et al., Comp Biochem Physiol Mol Integr Physiol 1998, 119:725.

In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as “D” or “deuterium”, the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

The term “isotopic enrichment factor” as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

The term “isotopologue” refers to a species in which the chemical structure differs from a specific compound of this invention only in the isotopic composition thereof.

The term “compound,” when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues in toto will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues in toto will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

The invention also provides salts of the compounds of the invention. A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

The term “pharmaceutically acceptable,” as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A “pharmaceutically acceptable counterion” is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, benzoic acid, fumaric acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfate, bisulfate, phosphate, monohydrogenophosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, malate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

The pharmaceutically acceptable salt may also be a salt of a compound of the present invention having an acidic functional group, such as a carboxylic acid functional group, and a base. Exemplary bases include, but are not limited to, hydroxide of alkali metals including sodium, potassium, and lithium; hydroxides of alkaline earth metals such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, organic amines such as unsubstit-
The compounds of the present invention (e.g., compounds of Formula I), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this invention can exist at either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present invention may exist as either a racemic mixture or a scalemic mixture, such as a mixture containing predominantly one stereoisomer, or as individual respective stereoisomers that are substantially free from another possible stereoisomer. The term “substantially free of other stereoisomers” as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

The term “stable compounds,” as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

“D” and “d” both refer to deuterium. “Stereoisomer” refers to both enantiomers and diastereomers. “Tert” and “t-” each refer to tertiary. “US” refers to the United States of America.

Substituted with deuterium or a cyclopentyl group not substituted with deuterium; or a pharmaceutically acceptable salt thereof, wherein:

R1 is selected from CH3, CH2D, CHD2, and CD3;
R2 is selected from the group consisting of methyl, isopropyl, cyclopentyl, cyclopropyl, 2-furanyl, trifluoromethyl, methoxyethyl, aminoethyl, dimethyloxymethyl, dimethylaminomethyl, dimethylamino-1-ethyl, 1-dimethyamino-ethyl, and 2-dimethylamino-ethyl, wherein R2 is optionally substituted with deuterium;
R3 is selected from CH3, CH2D, CHD2, CD3, CF3, CHF2, CH3F, CDF2, and CD2F;
R4 is an ethyl group substituted with zero to five deuterium, or a cyclopentyl group not substituted with deuterium; or a pharmaceutically acceptable salt thereof, wherein:

R1 is selected from CH3, CH2D, CHD2, and CD3;
R2 is selected from the group consisting of methyl, isopropyl, cyclopentyl, cyclopropyl, 2-furanyl, trifluoromethyl, methoxyethyl, aminoethyl, dimethyloxymethyl, dimethylaminomethyl, dimethylamino-1-ethyl, 1-dimethyamino-ethyl, and 2-dimethylamino-ethyl, wherein R2 is optionally substituted with deuterium;
R3 is selected from CH3, CH2D, CHD2, CD3, CF3, CHF2, CH3F, CDF2, and CD2F;
R4 is selected from CH2CH3, CD7CH3, CD2CH3, and CH3CD2; and

each Y is independently selected from H and D; and

ey are the same. In one aspect, Y6, Y7, and Y8 are each hydrogen.
In one embodiment of Formula I or Formula II, Y₁α and Y₁* are the same. In one aspect, Y₁α and Y₁* are both hydrogen. In another aspect, Y₁α and Y₁* are both deuterium.

In one embodiment of Formula I or Formula II, Y₃, Y₄ and Y₅ are the same. In one aspect, Y₃, Y₄ and Y₅ are each hydrogen.

In one embodiment of Formula I or Formula II, R₄ is CD₂CD₃. In one embodiment of Formula I or Formula II, R₂ is CH₃ or CD₃; R₃ is CH₃ or CD₃; Y₆, Y₇ and Y₈ are the same; Y₁α and Y₁* are the same; and Y₃, Y₄ and Y₅ are the same.

In one embodiment of Formula I or Formula II, R₁ is CH₃ or CD₃; R₂ is CH₃ or CD₃; R₃ is CH₃ or CD₃; R₄ is CD₂CD₃; Y₆, Y₇ and Y₈ are the same; Y₁α and Y₁* are the same; and Y₃, Y₄ and Y₅ are the same.

In one embodiment, the compound of Formula I is a compound of Formula Ia, having predominantly the (S) configuration at the carbon attached to Y₂; or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as defined for Formula I.

In one embodiment, the compound of Formula Ia is substantially free of other stereoisomers.

In one embodiment, the compound of Formula I is a compound of Formula Ib, having predominantly the (R) configuration at the carbon attached to Y₂; or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as defined for Formula I.

In one embodiment of Formula Ia or Formula Ib, R₄ is CD₂CD₃.

In one embodiment of Formula Ia or Formula Ib, R₁ is CH₃ or CD₃; R₂ is CH₃ or CD₃; R₃ is CH₃ or CD₃; R₄ is CD₂CD₃; Y₆, Y₇ and Y₈ are the same; Y₁α and Y₁* are the same; and Y₃, Y₄ and Y₅ are the same.

In one embodiment, the compound of Formula Ia or Formula Ib is selected from the group consisting of:

- Compound 100
- Compound 101
- Compound 102
In one embodiment, the compound of Formula I is selected from the group consisting of:

or a pharmaceutically acceptable salt of any of the foregoing.

In one embodiment, the compound is a compound of Formula Ia and is selected from the group consisting of:

or a pharmaceutically acceptable salt of any of the foregoing.
or a pharmaceutically acceptable salt of any of the foregoing.

One embodiment provides a compound that is predominantly the (S) enantiomer of compound 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, or 112 or a pharmaceutically acceptable salt of any of the foregoing.

One embodiment provides a compound that is predominantly the (S) enantiomer of compound 113, 114, 115, 116 or a pharmaceutically acceptable salt of any of the foregoing.

One embodiment provides a compound that is predominantly the (R) enantiomer of compound 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, or 112 or a pharmaceutically acceptable salt of any of the foregoing.

One embodiment provides a compound that is predominantly the (R) enantiomer of compound 113, 114, 115, 116 or a pharmaceutically acceptable salt of any of the foregoing.

In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above for a compound of Formula I, I(a), or I(b) is present at its natural isotopic abundance.

The synthesis of compounds of Formula I can be readily achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance in Man, H. W. et al., Journal of Medicinal Chemistry (2009), 52(6), 1522-1524; Muller, G. W. et al. Journal of Medicinal Chemistry (1996), 39(17), 3238-3240; WO2006/025991; AU2006/200033; WO2001/034606; U.S. Pat. No. 6,020,358; and U.S. Pat. No. 6,667,316.

Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Certain intermediates can be used with or without purification (e.g., filtration, distillation, sublimation, crystallization, trituration, solid phase extraction, and chromatography).

EXEMPLARY SYNTHESIS

Scheme 1: General Route to Compounds of Formula I.

Formula I
with lithium hexamethyldisilazide, followed by lithium dimethylsulfide and boron trifluoride etherate to afford racemic amine 11, which has a stereocenter at the carbon attached to Y2. If desired, racemic amine 11 may be resolved via treatment with an enantiopure acid in methanol. For example, treatment of racemic amine 11 with N-acetyl-L-leucine affords amine 11 as the S enantiomer, while treatment with N-acetyl-D-leucine affords amine 11 as the R enantiomer. Amine 11 may be used as the racemate, as the S enantiomer, or as the R enantiomer to yield compounds of Formula I upon treatment with anhydride 12 either neat or in a solvent such as acetic acid. One skilled in the art will appreciate that the use of appropriately deuterated intermediates and reagents in Scheme 1 results in the production of compounds of Formula I bearing various patterns of deuterium substitution.

For example, commercially-available dimethyl-d₆ sulfate may be used as reagent 17 in Scheme 2 to ultimately produce compounds of Formula I wherein R₃ is CD₃. In another example, commercially-available bromoethane-d₅ may be used as reagent 14 in Scheme 2 to ultimately produce compounds of Formula I wherein R₄ is —CD₂CD₃. Similarly, commercially-available bromoethane-2,2,2-d₃ and bromoethane-1,1-d₂ would also be of use in Scheme 2 to ultimately produce compounds of Formula I bearing various other patterns of deuterium substitution at R₄.

Scheme 2 depicts a preparation of aldehyde 10, which is a useful starting material for Scheme 1. As generally described in Li, Juren; et al. Flecheng Fluaxue (1993), 1(4), 333-40, appropriately-deuterated diol 13 is treated with appropriately-deuterated ethyl bromide 14 under phase transfer conditions to afford phenol 15. Reimer-Tiemann reaction of phenol 15 with chloroform provides aldehyde 16. Deuterated reagents and solvents may be useful in this step to maximize levels of isotopic incorporation. Alternatively, the tetrabuty-
Scheme 3 depicts a preparation of intermediate 12a, an example of intermediate 12 wherein X is C=O, and intermediate 12b, an example of intermediate 12 wherein X is CH3, CHD, or CD3. Nitrification of anhydride scaffold 18 is well known in the literature, for example in patent applications WO 2005051870, CN 17480138, and CN 1405143; and in literature articles including Chen, Zhi-min; et al. Hecheng Huaxue (2004). 12(2), 167-169, 173; Zhu, Zhi-jian; et al. Huaxue Shiji (2003). 25(5), 306, 308; Ma, S. L.; et al. Polish Journal of Chemistry (2002), 76(4), 511-517; and Culhane, P. J.; et al. Organic Syntheses (1927), 7, no pp. given. Use of appropriately-deuterated starting materials and reagents will produce deuterated versions of 19. According to the general methods described in US patent application US 2008234359, hydrogenation of 19 in the presence of palladium on carbon affords amine 20, which is then treated with appropriately-deuterated acetic anhydride 21 to provide intermediate 2a. According to the general methods of Wamser, C. C.; et al. J. Org. Chem. (1976), 41(17), 2929-31, intermediate 2a may be reduced with zinc and acid to provide intermediate 2b. Commercially-available DCl, acetic acid-d4, and acetic anhydride-d6 may be used in the final step to provide alternate patterns of deuterium incorporation.

For example, commercially-available 3-aminophthalic acid may be used in Scheme 3 as intermediate 20 to ultimately produce compounds of Formula I wherein Y6, Y7, and Y8 are all hydrogen. In another example, commercially-available acetic anhydride-d6 may be used in Scheme 3 as reagent 21 to ultimately yield compounds of Formula I wherein R2 is CD3. In yet another example, commercially-available phthalic acid-d4 anhydride may be used in Scheme 3 as anhydride 18 to ultimately provide compounds of Formula I wherein Y6, Y7, and Y8 are all deuterium.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

Compositions

The invention also provides compositions comprising an effective amount of a compound of Formula I (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and an acceptable carrier. The carrier(s) are “acceptable” in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Pharmacologically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as propanol sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypolyethylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradural) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, Md. (20th ed. 2000).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and aceite or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycercin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.
Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oeligenous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween; 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer’s solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz J D and Zafarani A C, U.S. Pat. No. 6,803,031, assigned to Alenza Molecular Delivery Corporation.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, poloxymers, polyoxyethylene polyoxypolypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polyoxyethylene 60, cetyl esters wax, cetaryl alcohol, 2-octyldecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Application of the patient therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, phoronic gel, stents, sustained drug release polymers or other device which provides for internal access.

Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethylsiloxane, polyacrylic lactone, polyethylene glycol, polylysatic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammalian host.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

Where an organ or tissue is accessible because of removal from the patient, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

In another embodiment, a composition of this invention further comprises a second therapeutic agent.

The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as apremilast. Such agents include those indicated as being useful in combination with apremilast, including but not limited to, those agents useful for the treatment of psoriasis, including plaque-type psoriasis and refractory psoriasis; sarcoidosis, including cutaneous sarcoidosis; psoriatic arthritis; Behçet’s Disease; prurigo nodularis; lupus, including cutaneous lupus; and uveitis, among others.

In one embodiment, the second therapeutic agent is an agent useful for the treatment of psoriasis or sarcoidosis.

In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term “associated with one another” as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dos-
therapy. This has the advantage of minimizing toxic side
monotherapeutic dosages of these second therapeutic agents
normally utilized in a monotherapy regime using just that
possibility of co-usage with other therapeutic treatments such
no more than 2.5 ng/kg/min per week for the remaining
treatment. In more specific embodiments the range is from
this invention can range from about 0.2 to 2000 mg per
treatment. In general health condition of the patient, excipient usage, the
duration or progression of the disorder being treated, prevent
the advancement of the disorder being treated, cause the
regression of the disorder being treated, or enhance or
improve the prophylactic or therapeutic effect(s) of another
therapy.

The interrelationship of dosages for animals and humans
(based on milligrams per meter squared of body surface) is
described in Freireich et al., Cancer Chemother. Rep, 1966,
50: 219. Body surface area may be approximately determined
from height and weight of the patient. See, e.g., Scientific
Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.
In one embodiment, an effective amount of a compound of
this invention can range from about 0.2 to 2000 mg per
treatment. In more specific embodiments the range is from
about 2 to 1000 mg or from 4 to 400 mg or most specifically
from 20 to 200 mg per treatment. Treatment typically is
administered at a rate of between 0.625 to 1.25 ng/kg/min.
The infusion rate can be increased in increments of no more
than 1.25 ng/kg/min per week for the first four weeks and then
no more than 2.5 ng/kg/min per week for the remaining
duration of infusion.

Effective doses will also vary, as recognized by those
skilled in the art, depending on the diseases treated, the sever-
ity of the disease, the route of administration, the sex, age and
general health condition of the patient, excipient usage, the
possibility of co-usage with other therapeutic treatments such
as use of other agents and the judgment of the treating physi-
cian. For example, guidance for selecting an effective dose
can be determined by reference to the prescribing information
for apremilast.

For pharmaceutical compositions that comprise a second
therapeutic agent, an effective amount of the second therapeu-
ic agent is between about 20% and 100% of the dosage
normally utilized in a monotherapy regime using just that
agent. Preferably, an effective amount is between about 70%
and 100% of the normal monotherapeutic dose. The normal
monotherapeutic dosages of these second therapeutic agents
are well known in the art. See, e.g., Wells et al. eds. Pharma-
cotherapy Handbook, 2nd Edition, Appleton and Lange,
Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon
Publishing, Loma Linda, Calif. (2000), each of which references
are incorporated herein by reference in their entirety.

It is expected that some of the second therapeutic agents
referred to above will act synergistically with the compounds
of this invention. When this occurs, it will allow the effective
dosage of the second therapeutic agent and/or the compound
of this invention to be reduced from that required in a mono-
therapy. This has the advantage of minimizing toxic side
effects of either the second therapeutic agent of a compound of
this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall
expense of compound preparation or formulation.

Methods of Treatment

In another embodiment, the invention provides a method of
inhibiting PDE4 in a subject, comprising administering to the
subject a compound of Formula I herein or a pharmaceu-
etically acceptable salt thereof.

In another embodiment, the invention provides a method of
reducing TNF-α levels in a subject, comprising administering
to the subject a compound of Formula I herein or a pharma-
aceutically acceptable salt thereof.

According to another embodiment, the invention provides a
method of treating a disease that is beneficially treated by
apremilast comprising the step of administering to a patient in
need thereof an effective amount of a compound of Formula
I or a pharmaceutically acceptable salt thereof or a composi-
tion of this invention. Such diseases are well known in the art
and are disclosed in, but not limited to the following patents
and published applications: WO2006/025991; AU2006/
200033; WO2001/034606; U.S. Pat. No. 6,020,358; and U.S.
Pat. No. 6,667,316.

Such diseases include, but are not limited to, septic shock,
sepsis, endotoxin shock, hemodynamic shock and sepsis syn-
drome, post ischemic reperfusion injury, malaria, mycobac-
terial infection, meningitis, psoriasis, including plaque-type
psoriasis and refractory psoriasis; sarcoidosis, including
cutaneous sarcoidosis; psoriatic arthritis; Behçet’s Disease;
Inflammatory bowel disease, aphthous ulcers, inflammatory
disease, endothelial injury, undesirable angiogenesis, inflam-
matory disease, arthritis, inflammatory bowel disease, aphthous ulcers,
I and adult respiratory distress syndrome, and AIDS.

In one particular embodiment, the method of this invention
is used to treat psoriasis or sarcoidosis.

Methods delineated herein also include those wherein the
patient is identified as in need of a particular stated treatment.
Identifying a patient in need of such treatment can be in the
judgment of a patient or a health care professional and can be
subjective (e.g. opinion) or objective (e.g. measurable by a
test or diagnostic method).

In another embodiment, any of the above methods of treat-
ment comprises the further step of co-administering to the
patient one or more second therapeutic agents. The choice of
two therapeutic agents may be made from any second
therapeutic agent known to be useful for co-administration
with apremilast. The choice of second therapeutic agent is
also dependent upon the particular disease or condition to be
treated. Examples of second therapeutic agents that may be
employed in the methods of this invention are those set forth
above for use in combination compositions comprising a
compound of this invention and a second therapeutic agent.

In particular, the combination therapies of this invention
include co-administering a compound of Formula I, or a
pharmaceutically acceptable salt thereof and a second therapeu-
ic agent for treatment of the following conditions: psor-
riasis, including plaque-type psoriasis and refractory psoriasis;
sarcoidosis, including cutaneous sarcoidosis; psoriatic
arthritis; Behçet’s Disease; prurigo nodularis; lupus, includ-
ing cutaneous lupus; and uveitis.

The term “co-administered” as used herein means that the
second therapeutic agent may be administered together with
a compound of this invention as part of a single dosage form
(such as a composition of this invention comprising a com-
 pound of the invention and a second therapeutic agent as
described above) or as separate, multiple dosage forms. Alter-
atively, the additional agent may be administered prior to,
consecutively with, or following the administration of a com-
 pound of this invention. In such combination therapy treat-
ment, both the compounds of this invention and the second
therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a patient does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said patient at another time during a course of treatment.

Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan’s purview to determine the second therapeutic agent’s optimal effective-amount range.

In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

In yet another aspect, the invention provides the use of a compound of Formula I or a pharmaceutical salt thereof alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment in a patient of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I or a pharmaceutical salt thereof for use in the treatment in a patient of a disease, disorder or symptom thereof delineated herein.

EXAMPLES

Example 1

Synthesis of (S)—N-(2-((1-aryl-2-(Methylsulfonyl)-1,3-dioxoisoindolin-4-yl)acetamide (Compound 1a)

Scheme 4. Preparation of Compound 1a.
Step 1. Ethyl 3-hydroxy-4-(methoxy-d3)-benzoate (23)

Commercially available ester 22 (10 g, 55 mmol) was mixed with CD3I (99 atom % D, Cambridge Isotopes; 8.1 g, 55 mol) and K2CO3 (7.59 g) in DMF and stirred at room temperature over a weekend. LCMS showed three peaks with masses consistent with starting material (20%), the desired monalkylated 23 (55%) product and the bisalkylated (23%) by-product. The reaction was filtered through a pad of Celite, washing with EtOAc, and the filtrate was concentrated to give 2.8 g of 23 (200 mL) and the solution was washed with water (5x50 mL), brine, dried (Na2SO4) and concentrated. The crude product was purified by chromatography on silica gel eluting with EtOAc/heptane (1:9 to 1:6) then further triturated from heptane to give 4.1 g (36%) of the desired 23.

Step 2. Ethyl 3-((ethoxy-d5)-4-(methoxy-d3)-benzoate (24)

23 (4.1 g, 20 mmol) was dissolved in DMF (10 mL) and K2CO3 (2.5 g) and CD3CD2Br (99 atom % D, Cambridge Isotopes; 4.7 g, 41 mmol) were added. The reaction flask was sealed and stirred at room temperature for 24 hr. LCMS showed the reaction was complete. The mixture was filtered through a pad of Celite, washing with MTBE, and the filtrate was concentrated to give approximately 3.8 g (81%) of 24 (purity approximately 90% by LCMS).

Step 3. (3-Ethoxy-d5)-4-(methoxy-d3)-phenyl-1,1-d2-methanol (25)

24 (3.8 g, 16.3 mmol) was dissolved in MTBE (50 mL) and LiAlD4 (98 atom % D, Cambridge Isotopes; 0.7 g, 17 mmol) was added. The reaction mixture was stirred at room temperature overnight. LCMS indicated the reaction was complete. Aqueous NH4Cl (20 mL) was added cautiously to quench the reaction and the mixture was filtered through a pad of Celite. The phases were separated and the aqueous phase was extracted with EtOAc (2x20 mL). The combined organic phases were dried (Na2SO4) and concentrated to give 2.05 g (68% for 2 steps) of 25 as a light yellow oil. This material was used directly in the next step.

Step 4. 3-(Ethoxy-d5)-4-(methoxy-d3)-benzaldehyde (10a)

25 (2.8 g, 16 mmol) was dissolved in EtOAc (30 mL). MnO2 (14 g, 160 mmol) was added and the dark mixture was stirred at room temperature overnight. LCMS showed complete consumption of the starting material. The mixture was passed through a pad of Celite, washing with EtOAc, and the filtrate was concentrated to give a yellow oil. The oil was purified via chromatography on silica gel eluting with 20% EtOAc/heptane to give 2.05 g (68% for 2 steps) of 10a as a white solid.

Step 5. 1-((Ethoxy-d5)-4-(methoxy-d3)-phenyl)-1-d2-(methylsulfonyl)ethanamine (11a)

Methyl sulfone (1 g, 10.7 mmol) was suspended in THF (70 mL) and cooled in an acetone/dry ice bath to below -70° C. n-BuLi (2.5 M in hexanes, 4.6 mL, 11.5 mmol) was added and the mixture stirred 30 minutes. In a separate flask, a solution of 10a (1.9 g, 10.0 mmol) in THF (20 mL) was cooled to 0° C. Lithium hexamethyldisilazide (LHMDS) (1M in THF, 12 mL) was added. After 15 minutes boron trifluoride etherate (2.8 mL, 22 mmol) was added and stirring was continued for another 5 minutes. This solution was then added to the methyl sulfone/n-BuLi solution, with cooling in an acetone/dry ice bath to below -70° C. via a syringe. An exotherm was observed. This mixture was allowed to warm to room temperature and was stirred overnight. After cooling in an ice-water bath, K2CO3 (8 g) was added followed by water (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2x20 mL). The combined organic solution was dried (Na2SO4) and concentrated to give a sticky oil. MTBE (30 mL) and aqueous HCl (4N, 30 mL) were added and the mixture stirred at room temperature for 2 hr to give a clear biphasic solution. The phases were separated and the organic solution extracted with aqueous HCl (4 N, 25 mL). To the combined aqueous phases was added aqueous NaOH (24%) until pH>12. The aqueous phase was extracted with EtOAc (3x50 mL). The organic phases were dried (Na2SO4) and concentrated to give a yellow solid. The solid was suspended in MTBE (20 mL) and stirred for one hour. Filtration under vacuum gave 1.2 g (36%) of 11a.

Step 6. (S)-1-((Ethoxy-d5)-4-(methoxy-d3)-phenyl)-1-d2-(methylsulfonyl)ethanamine N-acetyl leucine salt ((S)-11a)

11a (1.2 g, 4.25 mmol) was mixed with N-acetyl-L-leucine (0.44 g, 2.55 mmol) in MeOH (10 mL). This mixture was heated at 70° C. for 3 hr then stirred at room temperature overnight. The solid was collected by vacuum filtration and suspended in MeOH (15 mL). The mixture was stirred at 70° C. for 2 hr, then at room temperature overnight. The solid was collected and the MeOH trituration was repeated. A 600-mg portion (31%) of (S)-11a was isolated with >99% ee.

Step 7. (S)-N-(2-(1-d-1-(3-(Ethoxy-d5)-4-(methoxy-d3)-phenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide (Compound 113a)

(S)-11a (380 mg, 0.88 mmol) was mixed with known 12a (200 mg, 1 mmol; see US 20080234359) in acetic acid (6 mL) and heated at reflux for 24 hr to drive the reaction to completion. The mixture was concentrated and the colorless oil was re-dissolved in EtOAc (100 mL). The solution was washed with saturated aqueous NaHCO3 (20 mL), dried (Na2SO4) and concentrated. The crude product was purified by column chromatography on an Analogix system eluting with 0-3% MeOH/CH2Cl2 to provide 360 mg of 113a. 1H-NMR (300 MHz, CDCl3): δ 1.58 (s, 1H); 2.27 (s, 3H); 2.87 (s, 3H); 3.72 (d, J=14.3 Hz); 4.55 (d, J=14.5 Hz); 6.84 (d, J=9.8 Hz); 11.1.
Example 2

Synthesis of (S)—N (2-(2-(Methylsulfonyl)-1-(3-ethoxy-d5)-4-(methoxy-d2)phenyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide (Compound 107a)

Scheme 5. Preparation of Compound 107a.

Step 1. 3-Hydroxy-4-(methoxy-d3)-benzaldehyde (27)

Commercially available 3,4-dihydroxy-benzaldehyde 26 (10 g, 80 mmol) was dissolved in DMF (50 mL), K$_2$CO$_3$ (10 g) was added and the solution was cooled in an ice-water bath. CD$_3$I (99 atom % D, Cambridge Isotopes; 12.4 g, 84 mmol) was slowly added, then the reaction was stirred at room temperature overnight. The reaction was diluted with EtOAc (200 mL) and filtered through a pad of Celite. The filtrate was concentrated to give a dark oil. EtOAc (150 mL) and water (50 mL) were added and the layers were separated. The aqueous phase was adjusted to pH 6 by the slow addition of IN HCl and the mixture was extracted with EtOAc (2x100 mL). The combined organic solution was dried (Na$_2$SO$_4$) and concentrated. The crude material was purified by column chromatography on silica gel eluting with EtOAc/heptane (1:100 mL). The combined organic solution was dried (Na$_2$SO$_4$) and concentrated. The crude material was purified by column chromatography on silica gel eluting with EtOAc/heptane (1:50 mL). The combined organic solution was dried (Na$_2$SO$_4$) and concentrated. The crude material was purified by column chromatography on silica gel eluting with EtOAc/heptane (1:100 mL). The combined organic solution was dried (Na$_2$SO$_4$) and concentrated. The crude material was purified by column chromatography on silica gel eluting with EtOAc/heptane (1:200 mL).

Step 2. 3-(Ethoxy-d5)-4-(methoxy-d2)-benzaldehyde (10b)

27 (4.3 g, 27.7 mmol) was mixed with Cs$_2$CO$_3$ (15 g, 46 mmol) in acetone and cooled in an ice-water bath. Bromoethane-d$_2$ (99 atom % D, Cambridge Isotopes; 3.8 g, 33.6 mmol) was added and the reaction was stirred overnight. MTBE was added and the mixture was filtered through a pad of Celite. After concentrating, the crude product was purified...
Step 3. 1-(3-(Ethoxy-d5)-4-(methoxy-d3)-phenyl)-2-(methylsulfonyl)ethanamine (11b)

Methyl sulfone (1 g, 10.7 mmol) was suspended in THF (70 mL) and cooled in an acetone/dry ice bath to below −70°C. n-BuLi (2.5 M in hexanes, 11.9 mmol) was added and the mixture was stirred for about 30 minutes. In a separate flask, a solution of the aldehyde 10b (2 g, 10.6 mmol) in THF (20 mL) was cooled to 0°C. LHMDS (1M in THF, 12 mL) was added. After 15 minutes boron trifluoride etherate (2.8 mL, 22 mmol) was added and stirring was continued for another 5 minutes. This solution was then added to the methyl sulfone/n-BuLi solution, with cooling in an acetone/dry ice bath at below −70°C., via a syringe. An exotherm was observed. This mixture was allowed to warm to room temperature and stirred overnight. After cooling in an ice-water bath, K2CO3 (8 g) was added followed by water (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2x20 mL). The combined organic solution was dried (Na2SO4) and concentrated to give a sticky oil. MTBE (30 mL) and aqueous HCl (4N, 25 mL) were added and the mixture was stirred at room temperature for 2 hr to give a clear biphasic solution. The phases were separated and the organic phase was extracted with aqueous HCl (4N, 25 mL). To the combined aqueous phases was added aqueous NaOH (24%) to raise the pH above 12. The solution was extracted with EtOAc (3x50 mL). The combined organic solution was dried (Na2SO4), and concentrated to give a yellow solid. The solid was suspended in MTBE (20 mL) and stirred for one hour. Filtration under vacuum gave 1.2 g (38%) of 11b as a light yellow solid.

Step 4. (S)-l-(3-(Ethoxy-d5)-4-(methoxy-d3)-phenyl)-2-(methylsulfonyl)ethanamine N-acetyl-L-leucine salt ((S)-11b)

11b (1.05 g, 3.73 mmol) was mixed with N-acetyl-L-leucine (0.39 g, 2.24 mmol) in MeOH (6 mL). This mixture was heated at 70°C for 3 hr then stirred at room temperature overnight. The solid was collected by vacuum filtration and was suspended in MeOH (15 mL). The suspension was stirred at 70°C. for 2 hr then at room temperature overnight. The solid was collected and the MeOH trituration was repeated. A 400-mg portion (23%) of (S)-11b N-acetyl-L-leucine salt was obtained with >98% ee.

Step 5. (S)—N-(2-(1-(3-(Ethoxy-d5)-4-(methoxy-d3)-phenyl)ethyl)-1,3-dioxoisoinodolin-4-yl)acetamide (Compound 107a)

(S)-11b N-acetyl-L-leucine salt (220 mg, 0.5 mmol) was mixed with known 12a (123 mg, 0.6 mmol) in acetic acid (5 mL) and heated at reflux for 24 hr to drive the reaction to near completion. The mixture was concentrated, the colorless oil was dissolved in EtOAc (100 mL) and the solution was washed with saturated aqueous NaHCO3 (20 mL). The organic phase was dried (Na2SO4) and concentrated. The crude product purified by column chromatography on an Analogix system eluting with 0-70% EtOAc/heptane to afford 210 mg (89%) of 107a. 1H-NMR (75 MHz, CDCl3): δ 24.97, 41.66, 48.60, 54.55, 55.96, 76.58, 77.01, 77.43, 11.48, 112.40, 115.14, 118.25, 120.29, 125.00, 129.26, 131.07, 136.14, 137.66, 148.70, 149.79, 167.51, 169.17, 169.53. HPLC (method: 50 mm 3 μm Waters Atlantis 13 2.1 column—gradient method 5-95% ACN+0.1% formic acid in 14 min with 4 min hold at 95% ACN+0.1% formic acid; wavelength: 305 nm); retention time: 6.02 min; >98% purity. Chiral HPLC (method: Chiralpak AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.01% diethylamine for 40 minutes at 1.00 mL/min; wavelength: 254 nm); retention time: 1.27 min (major enantiomer); >99% ee purity. MS (M+Na): 488.1. Elemental Analysis (C22H21D3N2OτS): Calculated: C=56.76, H=5.20, N=6.02, S=6.89. Found: C=56.74, H=5.43, N=5.70, S=6.51.

Example 3

Synthesis of (S)—N-(2-(1-(Methylsulfonyl)-1-(3-ethoxy-4-(methoxy-d3)phenyl)ethyl)-1,3-dioxoisoinodolin-4-yl)acetamide (Compound 114a)

Scheme 6. Preparation of Compound 114a.
Step 1. 3-Ethoxy-4-(methoxy-d3)-benzaldehyde (10c)

A mixture of commercially available 16a (5 g, 30 mmol) and Cs₂CO₃ (15 g, 46 mmol) in acetone was cooled in an ice-water bath. (CD₃)₂SO₄ (99 atom % D, Cambridge Isotopes; 2.7 mL, 30 mmol) was added and the reaction was allowed to warm slowly to room temperature and was stirred overnight. The mixture was filtered through a pad of Celite and concentrated to give 5.7 g (approx 100%) of 10c.

Step 2. L-(3-Ethoxy-4-(methoxy-d3)phenyl)-2-(methylsulfonyl)ethanamine (11c)

Methyl sulfone (3 g, 32.1 mmol) was suspended in THF (280 mL) and cooled in an acetone/dry ice bath to below -70° C. n-BuLi (2.5 M in hexanes, 13.6 mL, 35.7 mmol) was added and the reaction was allowed to warm slowly to room temperature and was stirred overnight. The mixture was filtered through a pad of Celite and concentrated to give 5.7 g (approx 100%) of 10c.

Step 2. 1-(3-Ethoxy-4-(methoxy-d3)phenyl)-2-(methylsulfonyl)ethanamine (11c)

Methyl sulfone (3 g, 32.1 mmol) was suspended in THF (280 mL) and cooled in an acetone/dry ice bath to below -70° C. n-BuLi (2.5 M in hexanes, 13.6 mL, 35.7 mmol) was added and the reaction was allowed to warm slowly to room temperature and was stirred overnight. The mixture was filtered through a pad of Celite and concentrated to give 5.7 g (approx 100%) of 10c.

Step 3. (S)-L-(3-Ethoxy-4-(methoxy-d3)-phenyl)-2-(methylsulfonyl)ethanamine N-acetyl-L-leucine salt ((S)-11c)

11c (2.3 g, 8.17 mmol) was mixed with N-acetyl-L-leucine (0.78 g, 4.48 mmol) in MeOH (12 mL). The mixture was heated at 70° C for 3 hr then stirred at room temperature overnight. The solid was collected by vacuum filtration, suspended in MeOH (12 mL) and stirred at 70° C for 2 hr, then at room temperature overnight. The solid was collected and the MeOH trituration was repeated. A 1-g portion (28.8%) of (S)-11c N-acetyl-L-leucine salt was obtained with >98% ee.

Step 4. (S)-N-(2-(L-(3-Ethoxy-4-(methoxy-d3)-phenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide (114a)

(S)-11c (0.97 g, 2.2 mmol) was mixed with known 12a (470 mg, 2.5 mmol) in acetic acid (20 mL) and heated at reflux for 24 hr to drive the reaction to near completion. The mixture was concentrated, the colorless oil was dissolved in EtOAc (200 mL) and the solution was washed with saturated NaHCO₃ (40 mL). The organic phase was dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography on an Analogix system eluting with 0-70% EtOAc/heptane to afford 0.7 g (68%) of 114a. ¹H-NMR (300 MHz, CDCl₃): δ 1.47 (t, J=7.0, 3H), 1.61 (s, 1H), 2.26 (s, 3H), 2.87 (s, 3H), 3.72 (dd, J=4.6, 14.4, 1H), 4.11 (q, J=6.9, 14.0, 2H), 4.55 (dd, J=10.5, 14.4, 1H), 5.87 (dd, J=4.4, 10.6, 1H), 6.84 (d, J=8.7, 1H), 7.10 (d, J=6.5, 2H), 7.49 (d, J=7.3, 1H), 7.65 (t, J=7.7, 1H), 8.76 (d, J=8.5, 1H), 9.46 (s, 1H). ¹³C-NMR (75 MHz, CDCl₃): δ 14.70, 24.96, 41.65, 48.59, 54.54, 64.55, 111.46, 112.44, 115.14, 118.25, 120.32, 125.00, 129.24, 131.07, 136.14, 137.66, 148.67, 149.79, 157.01, 169.17, 169.53. HPLC (method: 50 mm 3 μm Waters Atlantis T3 2.1 column—gradient method 5-95% ACN+0.1% formic acid in 14 min with 4 min hold at 95% ACN+0.1% formic acid; wavelength: 305 nm): retention time: 6.03 min; 97.4% purity. ChiralHPLC (method: Chiralpak AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.01% diethylamine for 40 minutes at 1.00 mL/min; wavelength: 254 nm): retention time: 12.69 min (major enantiomer); 39.03 min (minor enantiomer); >99% ee purity. MS (M+Na):
Elemental Analysis (C$_{22}$H$_{21}$D$_3$N$_2$O$_7$S): Calculated: C=57.01, H=5.22, N=6.04, S=6.92. Found: C=57.68, H=5.63, N=5.52, S=6.33.

Example 4

Synthesis of (S)—N-(2-(2-Methylsulfonyl)-1-(3-(ethoxy-d$_5$)-4-(methoxy)phenyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide (Compound 110a)

Scheme 7. Preparation of Compound 110a.

Step 1. 3-(Ethoxy-d$_5$)-4-methoxy-benzaldehyde (10d)

Commercially available 29 (5 g, 30 mmol) was mixed with Cs$_2$CO$_3$ (15 g, 46 mmol) in acetone and cooled in an ice-water bath. Bromoethane-d$_5$ (99 atom % D, Cambridge Isotopes; 3.8 g, 33.6 mmol) was added and the reaction was allowed to warm slowly to room temperature and was stirred overnight. The reaction was diluted with MTBE, filtered through a pad of Celite, and concentrated to give 5.5 g (approx 100%) of 10d.

Step 2. 1-(3-(Ethoxy-d$_5$)-4-methoxy-phenyl)-2-(methylsulfonyl)ethanamine (11d)

Methyl sulfone (2.76 g, 29.5 mmol) was suspended in THF (250 mL) and cooled in an ice-water bath at below -70° C. n-BuLi (2.5 M in hexanes, 12.5 mL, 31 mmol) was added and the mixture was stirred for about 30 minutes. In a separate flask a solution of the aldehyde 10d (5.25 g, 27.6 mmol) in THF (50 mL) was cooled to 0° C. LHMDS (1M in THF, 31.7 mL) was added. After 15 minutes boron trifluoride etherate (7.36 mL, 57.8 mmol) was added and the mixture was stirred another 5 minutes. This solution was then added to the methyl sulfone/n-BuLi solution, with cooling in an ice-water bath at below -70° C, via a syringe. An exotherm was observed. This mixture was allowed to warm to room temperature and was stirred overnight. After cooling in an ice-water bath, K$_2$CO$_3$ (24 g) was added followed by water (150 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3x150 mL). The combined organic solution was dried (Na$_2$SO$_4$) and concentrated to give a sticky oil. MTBE (90 mL) and aqueous HCl (4N, 90 mL) were added and the mixture was stirred at room temperature for 2 hr to give a clear biphasic solution. The phases were separated and the organic phase was extracted with aqueous HCl (4 N, 75 mL). To the combined aqueous phases was added aqueous NaOH (24%) to raise the pH above 12. The mixture was extracted with EtOAc (3x150 mL). The combined organic solution was dried (Na$_2$SO$_4$), and concentrated to give a yellow solid. The solid was suspended in MTBE (60 mL) and stirred for one hour. Filtration under vacuum afforded 2.7 g (34.2%) of 11d as a light yellow solid.

Step 3. ((S)-1-((3-(Ethoxy-d$_5$)-4-methoxy-phenyl))-2-(methylsulfonyl)ethanamine N-acetyl L-leucine salt ((S)-11d)

11d (2.6 g, 9.33 mmol) was mixed with N-acetyl-L-leucine (0.98 g, 5.56 mmol) in MeOH (15 mL). This mixture was
heated at 70°C for 3 hr then stirred at room temperature overnight. The solid was collected by vacuum filtration and suspended in MeOH (15 mL). The suspension was stirred at 70°C for 2 hr then at room temperature overnight. The solid was collected and the MeOH trituration was repeated. A 1-g portion (23%) of (S)-11d N-acetyl-L-leucine salt was obtained with >98% ee.

Step 4. (S)—N-(2-(1-(3-(Ethoxy-d5)-4-methoxy-phenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisodindolin-4-yl)acetamide (110a)

(S)-11d (1.4 g, 3.2 mmol) was mixed with known 12a (0.77 g, 3.84 mmol) in acetic acid (20 mL) and heated at reflux for 24 hr to drive the reaction to near completion. The mixture was concentrated, the colorless oil was dissolved in EtOAc (200 mL) and the solution was washed with saturated NaHCO3 (40 mL). The organic layer was dried (Na2SO4) and concentrated. The crude product was purified by column chromatography on an Analogix system eluting with 0-70% EtOAc/heptane (in 1 hr) to afford 1.2 g (80%) of 110a.

Example 5
Synthesis of Intermediate 12b

Commercially available 4-aminoisobenzofuran-1,3-dione (5 g, 50.6 mmol) was suspended in acetic anhydride-de (98 atom % D, Cambridge Isotopes; 10 g) and heated at reflux for 3 hr, then stirred at room temperature overnight. The solution was cooled to 0°C and filtered, then the solid was washed with MTBE and dried to provide 2.5 g of 12b.
Example 7

(S)—N-(2-(1-(3-(Ethoxy-d5)-4-methoxy-d3)-phenyl)-2-((methyl-d3)-sulfonyl)-2,2-d2-ethyl)-1,3-dioxoisindolin-4-yl)acetamide (Compound 116a)


Step 1. 1-(3-(Ethoxy-d5)-4-(methoxy-d3)-phenyl)-2-((methyl-d3)-sulfonyl)-2,2-d2-ethanamine (Compound 116a)

Methyl sulfone-d6 (99 atom % D, Isotec; 1 g, 10.0 mmol) was suspended in THF (70 mL) and cooled in an acetone/dry ice bath to below -70° C. n-BuLi (2.5 M in hexanes, 4.4 mL, 11 mmol) was added and the mixture was stirred about 30 minutes. In a separate flask, a solution of the aldehyde 10b (1.91 g, 10.0 mmol; see Scheme 5) in THF (20 mL) was cooled to 0° C. LHMDS (1M in THF, 11 mL) was added. After 15 minutes boron trifluoride etherate (2.8 mL, 22 mmol) was added and stirring was continued for another 5 minutes. This solution was added to the methyl sulfone-d6/n-BuLi solution, with cooling in an acetone/dry ice bath to below -70° C., via a syringe. An exotherm was observed. The mixture was allowed to warm to room temperature and was stirred overnight. After cooling in an ice-water bath, K2CO3 (8 g) was added followed by water (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic solution was dried (Na2SO4) and concentrated to give a sticky oil. MTBE (30 mL) and aqueous HC1 (4N, 30 mL) were added and the mixture was stirred at room temperature for 2 hr to give a clear biphasic solution. The phases were separated and the organic phase was extracted with aqueous HC1 (4N, 25 mL). To the combined aqueous phases was added aqueous NaOH (24%) to raise the pH above 12. The solution was extracted with EtOAc (3x50 mL). The combined organic solution was dried (Na2SO4) and concentrated to give a yellow solid. The solid was suspended in MTBE (20 mL) and stirred for one hour. Filtration under vacuum gave 1.2 g (37%) of 11e as a light yellow solid.

1H NMR and LCMS showed some loss of isotopic purity alpha to the sulfone. This D-to-H exchange likely occurred during the acid/base extraction. Use of deuterated solvents is preferred throughout the workup.

The less isotopically pure material was dissolved in MeOD (99 atom % D, Cambridge Isotopes; 30 mL) and K2CO3 (0.5 g) was added. This mixture was heated at 70° C. for 6 hr and then concentrated to dryness. Fresh MeOD (30 mL) was added and the mixture heated to 70° C. overnight. The cooled solution was diluted with EtOAc (100 mL) and the mixture was filtered. The filtrate was concentrated and re-dissolved in EtOAc (100 mL). The solution was washed with D2O (99.9 atom % D, Cambridge Isotopes; 20 mL). The organic phase was dried (Na2SO4) and concentrated to give approximately 1 g of 11e with high isotopic purity restored.

Step 2. 1-(3-(Ethoxy-d5)-4-(methoxy-d3)-phenyl)-2-((methyl-d3)-sulfonyl)-2,2-d2-ethanamine N-acetyl-L-leucine salt (S)-11e

11e (630 mg, 2.2 mmol) was mixed with N-acetyl-L-leucine (0.23 g, 1.32 mmol) in MeOD (99 atom % D, Cambridge
Isotopes; 6 mL). This mixture was heated at 70°C for 3 hr then stirred at room temperature overnight. The solid was collected by vacuum filtration and suspended in MeOH (6 mL). The mixture was stirred at 70°C for 2 hr then at room temperature overnight. The solid was collected and the MeOH trituration was repeated. A 300-μg portion (29%) of(S)-11e N-acetyl-L-leucine salt was obtained with >99% ee.

Step 3. (S)—N-(2-(1-(3-(Ethoxy-d5)-4-(methoxy-d2)-phenyl)-2-((methyl-d1)-sulfonyl)-2,2-d1-ethyl)-1,3-dioxoisooindolin-4-yl)acetamide (116a)

(S)-11e N-acetyl-L-leucine salt (280 mg, 0.62 mmol) was mixed with known 12a (145 mg, 0.7 mmol) in acetic acid-d (99 atom % D, Aldrich; 5 mL) and heated to reflux for 24 hr to drive the reaction to near completion. The mixture was concentrated and the colorless oil was dissolved in EtOAc (100 mL). The solution was washed with NaHCO3 (20 mL), dried (Na2SO4) and concentrated. The crude product was purified by column chromatography on an Analogix system eluting with 0-3% MeOH/CH2Cl2 to provide 245 mg (84%) of116a. 1H-NMR (300 MHz, CDCl3): δ 1.57 (s, 1H), 2.26 (s, 3H), 5.86 (s, 1H), 6.84 (d, J=6.8, 1H), 7.10 (d, J=6.8, 2H), 7.49 (d, J=6.4, 1H), 7.65 (t, J=7.9, 1H), 8.76 (d, J=8.5, 1H), 9.46 (s, 1H). 13C-NMR (75 MHz, CDCl3): δ 24.97, 48.43, 111.45, 112.40, 115.14, 114.25, 120.28, 125.00, 129.22, 131.07, 136.14, 137.66, 148.70, 149.79, 167.52, 169.17, 169.54. HPLC (method: 50 mm 3 μm Waters Atlantis T3 2.1 column—gradient method 5-95% ACN+0.1% formic acid in 14 min with 4 min hold at 95% ACN+0.1% formic acid; wavelength: 305 nm); retention time: 5.97 min; 99.7% purity. MS (M+H): 474.3. Elemental Analysis (C22HuD13N2O7S); calculated: C=55.80, H=5.11, N=5.92. Found: C=52.73, H=4.73, N=5.43.

EXAMPLE

Evaluation of Metabolic Stability

Microsomal Assay:

Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, Kans.). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride (MgCl2), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

Determination of Metabolic Stability: 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 μg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM MgCl2. The diluted microsomes are added to wells of a 96-well deep-well plate in triplicate. A 10 μL aliquot of the 12.5-50 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM MgCl2. The reaction mixtures are incubated at 37°C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4°C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for apremilast and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

Data Analysis:

The in vitro t1/2 values for test compounds are calculated from the slopes of the linear regression of % parent remaining (In) vs incubation time relationship.

\[ k = \frac{\text{slope of linear regression of % parent remaining}}{\text{inhای incubation time}} \]

Data analysis is performed using Microsoft Excel Software.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

I claim:

1. A compound of Formula 1:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

- \( R^1 \) is selected from \( CH_3, CH_2D, CHD_2, \) and \( CD_3 \);
- \( R^2 \) is \( CH_2 \) or \( CD_2 \);
- \( R^3 \) is \( CD_3 \);
- \( R^4 \) is an ethyl group substituted with zero to five deuterium, or is a cyclopentyl group substituted with zero to nine deuterium;
- \( X = C=O \);
- each of \( Y^1 = Y^2, Y^3, Y^4, Y^5, Y^6 \) and \( Y^7 \) and \( Y^8 \) is independently selected from \( H \) and \( D \); and
- wherein the isotopic enrichment factor for each designated deuterium atom is at least 3500.

2. The compound of claim 1 wherein the isotopic enrichment factor for each designated deuterium atom is at least 6333.3.

3. The compound of claim 1, wherein \( Y^6 \) and \( Y^7 \) are the same; \( Y^1 = Y^4 \) and \( Y^16 \) are the same; and \( Y^2, Y^3 \) and \( Y^5 \) are the same.
4. The compound of claim 3, wherein the compound of Formula I is a compound of Formula II:

or a pharmaceutically acceptable salt thereof, wherein:
R¹ is selected from CF₃ and CD₃; and
R⁴ is selected from CH₂CH₃, CD₂CD₃, CD₂CH₃, and CH₂CD₃.

5. The compound of claim 3, wherein the compound of Formula I is a compound of Formula Ia, having predominantly the (S) configuration at the carbon attached to Y₂:

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 3, wherein the compound of Formula I is a compound of Formula Ib, having predominantly the (R) configuration at the carbon attached to Y₂:

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein Y₆, Y₇ and Y₈ are the same.

8. The compound of claim 1, wherein Y¹α and Y¹β are the same.

9. The compound of claim 1, wherein Y³, Y⁴ and Y⁵ are the same.

10. The compound of claim 1, wherein R¹ is CH₃ or CD₃.

11. The compound of claim 1, wherein R⁴ is CD₂CD₃.

12. A compound selected from the group consisting of:

Compound 100

Compound 101

Compound 102

Compound 103
or a pharmaceutically acceptable salt of any of the foregoing, wherein the isotopic enrichment factor for each designated deuterium atom is at least 3500.

13. A compound of claim 12, wherein the isotopic enrichment factor for each designated deuterium atom is at least 6333.3.

14. A compound of claim 13, having predominantly the (S) configuration.

15. A compound of claim 12, having predominantly the (R) configuration.

16. A compound selected from the group consisting of:
19. The compound of claim 16 wherein the isotopic enrichment factor for each designated deuterium atom is at least 5000.

20. The compound of claim 16 wherein the isotopic enrichment factor for each designated deuterium atom is at least 5500.

21. The compound of claim 16 wherein the isotopic enrichment factor for each designated deuterium atom is at least 6000.

22. The compound of claim 16 wherein the isotopic enrichment factor for each designated deuterium atom is at least 6333.3.

23. The compound of claim 16 wherein the isotopic enrichment factor for each designated deuterium atom is at least 6466.7.

24. The compound of claim 16 wherein the isotopic enrichment factor for each designated deuterium atom is at least 6600.

25. The compound of claim 16 wherein the isotopic enrichment factor for each designated deuterium atom is at least 6633.3.

26. A compound of claim 1, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

27. A composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt of said compound; and an acceptable carrier.

28. A method of inhibiting PDE4 in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

29. A method of reducing TNF-α levels in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

30. A method of treating a disease selected from the group consisting of psoriasis, sarcoidosis, psoriatic arthritis, Behçet’s Disease, prurigo nodularis, lupus, rheumatoid arthritis, and rheumatoid spondylitis in a patient in need thereof comprising administering to the patient an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

31. The method of claim 30 wherein the condition is psoriasis or sarcoidosis.

32. The method of claim 31 wherein psoriasis is plaque-type psoriasis or refractory psoriasis.

33. The method of claim 32 wherein sarcoidosis is cutaneous sarcoidosis.

34. The method of claim 30 wherein lupus is cutaneous lupus.

35. The method of claim 30 wherein the disease is selected from Behçet’s Disease and rheumatoid arthritis.

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