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(54) Title: ISOTOPOLOGUES OF POMALIDOMIDE

(57) Abstract: Provided herein are pomalidomide, which is enriched with isotopes such as deuterium. Pharmaceutical compositions comprising the isotopes-enriched compounds, and methods of using such compounds are also provided.

ISOTOPOLOGUES OF POMALIDOMIDE

[0001] This application claims priority to U.S. Provisional Application Nos. 61/500,053, filed June 22, 2011, and 61/652,053, filed May 25, 2012, the entireties of which are incorporated herein by reference.

1. FIELD

[0002] Provided herein are isotopologues of pomalidomide, compositions comprising the isotopologues, methods of making the isotopologues, and methods of their use for treatment or prevention of diseases and conditions including, but not limited to, inflammatory diseases, autoimmune diseases, and cancers.

2. BACKGROUND

[0003] Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance. Roitt, I., Brostoff, J and Kale, D., Immunology, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

[0004] There is an enormous variety of cancers which are described in detail in the medical literature. Examples include cancer of the lung, colon, rectum, prostate, breast, brain, and intestine. The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations (e.g., people infected with AIDS or excessively exposed to sunlight) grow. However, options for the treatment of cancer are limited. For example, in the case of blood cancers (e.g., multiple myeloma), few treatment options are available, especially when conventional chemotherapy fails and bone-marrow transplantation is not an option. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

[0005] Many types of cancers are associated with new blood vessel formation, a process known as angiogenesis. Several of the mechanisms involved in tumor induced angiogenesis have been elucidated. The most direct of these mechanisms is the secretion by the tumor cells of cytokines with angiogenic properties. Examples of these cytokines include acidic and basic fibroblastic growth factor (a,b FGF), angiogenin, vascular endothelial growth factor (VEGF), and TNF α. Alternatively, tumor cells can release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (e.g., b FGF). Angiogenesis can also be induced indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (e.g., TNF α, b-FGF).

[0006] A variety of other diseases and disorders are also associated with, or characterized by, undesired angiogenesis. For example, enhanced or unregulated angiogenesis has been implicated in a number of diseases and medical conditions including, but not limited to, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, rubeosis (neovascularization of the angle), viral diseases, genetic diseases, inflammatory diseases, allergic diseases, and autoimmune diseases. Examples of such diseases and conditions include, but are not limited to: diabetic retinopathy; retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasia; arthritis; and proliferative vitreoretinopathy.

[0007] Accordingly, compounds that can control angiogenesis or inhibit the production of certain cytokines, including TNFα, may be useful in the treatment and prevention of various diseases and conditions.

[0008] Current cancer therapy may involve surgery, chemotherapy, hormonal therapy and/or radiation treatment to eradicate neoplastic cells in a patient (*see*, *e.g.*, Stockdale, 1998, *Medicine*, vol. 3, Rubenstein and Federman, eds., Chapter 12, Section IV). Recently, cancer therapy could also involve biological therapy or immunotherapy. All of these approaches pose significant drawbacks for the patient. Surgery, for example, may be contraindicated due to the health of a patient or may be unacceptable to the patient. Additionally, surgery may not completely remove neoplastic tissue. Radiation therapy is only effective when the neoplastic tissue exhibits a higher sensitivity to radiation than normal tissue. Radiation therapy can also often elicit serious side effects. Hormonal therapy is rarely given as a single agent. Although hormonal therapy can be effective, it is often used to prevent or delay recurrence of cancer after

other treatments have removed the majority of cancer cells. Biological therapies and immunotherapies are limited in number and may produce side effects such as rashes or swellings, flu-like symptoms, including fever, chills and fatigue, digestive tract problems or allergic reactions.

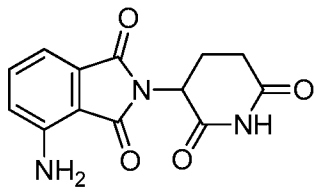
[0009] With respect to chemotherapy, there are a variety of chemotherapeutic agents available for treatment of cancer. A majority of cancer chemotherapeutics act by inhibiting DNA synthesis, either directly, or indirectly by inhibiting the biosynthesis of deoxyribonucleotide triphosphate precursors, to prevent DNA replication and concomitant cell division. Gilman et al., Goodman and Gilman's: The Pharmacological Basis of Therapeutics, Tenth Ed. (McGraw Hill, New York).

[0010] Despite availability of a variety of chemotherapeutic agents, chemotherapy has many drawbacks. Stockdale, Medicine, vol. 3, Rubenstein and Federman, eds., ch. 12, sect. 10, 1998. Almost all chemotherapeutic agents are toxic, and chemotherapy causes significant, and often dangerous side effects including severe nausea, bone marrow depression, and immunosuppression. Additionally, even with administration of combinations of chemotherapeutic agents, many tumor cells are resistant or develop resistance to the chemotherapeutic agents. In fact, those cells resistant to the particular chemotherapeutic agents used in the treatment protocol often prove to be resistant to other drugs, even if those agents act by different mechanism from those of the drugs used in the specific treatment. This phenomenon is referred to as pleiotropic drug or multidrug resistance. Because of the drug resistance, many cancers prove or become refractory to standard chemotherapeutic treatment protocols.

[0011] Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, hepain and steroids have been proposed to be useful in the treatment of certain specific diseases. (Taylor *et al.*, *Nature* 297:307 (1982); Folkman *et al.*, *Science* 221:719 (1983); and U.S. Pat. Nos. 5,001,116 and 4,994,443).

[0012] Still, there is a significant need for safe and effective methods of treating, preventing and managing cancer and other diseases and conditions, including for diseases that are refractory to standard treatments, such as surgery, radiation therapy, chemotherapy and hormonal therapy, while reducing or avoiding the toxicities and/or side effects associated with the conventional therapies.

[0013] Pomalidomide has the chemical structure:



and is chemically described variously as: 4-amino-2-(2,6-dixopiperidin-3-yl)isoindoline-1,3-dione; 3-(4-amino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione; 3-(4-amino-1,3-dioxoisoindolin-2-yl)piperidine-2,6-dione; 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline; 3-(1,3-dioxo-4-aminoisoindolin-2-yl)-piperidine-2,6-dione; among other chemical names. Pomalidomide and compositions comprising pomalidomide have utility for, *inter alia*, treatment of certain cancers (*e.g.*, multiple myeloma, myelodyplastic syndrome, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma) and other various diseases and disorders.

3. SUMMARY

[0014] Embodiments provided herein encompass particular isotopologues of pomalidomide, or a pharmcuetically acceptable stereoisomer thereof. Certain embodiments encompass mixtures of isotopologues. Certain embodiments encompass methods of synthesizing, isolating, or characterizing the isotopologues.

[0015] In certain embodiments, provided herein are pharmaceutical compositions and single unit dosage forms comprising one or more isotopologues of pomalidomide, or pharmaceutically acceptable stereoisomers thereof. Certain embodiments provide methods for the treatment or prevention of particular diseases or disorders, which comprise administering to a patient a therapeutically or prophylactically effective amount of an isotopologue of pomalidomide.

4. DETAILED DESCRIPTION

4.1 DEFINITIONS

[0016] The descriptions of the terminology provided below apply to the terms as used herein and unless otherwise specified.

[0017] The term "compound" includes salts and solvates (*e.g.*, hydrates) thereof.

[0018] The term "isotopic composition" refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural isotopic composition.

[0019] The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. As used herein, an "isotopologue" is an isotopically enriched compound.

[0020] The term "isotopic enrichment" refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic composition. For example, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%.

[0021] The term "isotopic enrichment factor" refers to the ratio between the isotopic composition and the natural isotopic composition of a specified isotope.

[0022] With regard to the compounds provided herein, when a particular atomic position is designated as having deuterium or "D," it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of, in particular embodiments, at least 1000 (15% deuterium incorporation), at least 2000 (30% deuterium incorporation), at least 3000 (45% deuterium incorporation), at least 3500 (52.5% deuterium incorporation), 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), at least 6466.7 (97% deuterium incorporation), at least

6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium atom.

[0023] The isotopic enrichment and isotopic enrichment factor of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[1] As used herein, and unless otherwise specified, the term "stereoisomer" encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds provided herein.

[2] As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound, greater than about 98% by weight of one stereoisomer of the compound and less than about 2% by weight of the other stereoisomers of the compound or greater than about 99% by weight of one stereoisomer of the compound and less than about 1% by weight of the other stereoisomers of the compound.

[3] As used herein and unless otherwise indicated, the term "stereomerically enriched" means a composition that comprises greater than about 55% by weight of one stereoisomer of a compound, greater than about 60% by weight of one stereoisomer of a compound, greater than about 70% by weight, or greater than about 80% by weight of one stereoisomer of a compound.

[0024] As used herein, and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound

having one chiral center. Similarly, the term "enantiomerically enriched" means a stereomerically enriched composition of a compound having one chiral center.

[0025] The terms “treat,” “treating” and “treatment” refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the term refers to the administration of a compound provided herein to a patient subsequent to the onset of a disease provided herein.

[0026] The terms “prevent,” “preventing” and “prevention” refer to the prevention of the onset, recurrence or spread of a disease or disorder, or of one or more symptoms thereof. In some embodiments, the term refers to the administration of a compound provided herein to a subject who is at a risk of one or more of the diseases provided herein prior to the onset of the diseases. In this regard, the term “prevention” may be equivalent to the term “prophylaxis” or “prophylactic treatment.”

[0027] The terms “manage,” “managing” and “management” refer to preventing or slowing the progression, spread or worsening of a disease or disorder, or of one or more symptoms thereof. In certain cases, the beneficial effects that a subject derives from a prophylactic or therapeutic agent do not result in a cure of the disease or disorder.

[0028] A “therapeutically effective amount” of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or disorder, or to delay or minimize one or more symptoms associated with the disease or disorder. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of the disease or disorder. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or disorder, or enhances the therapeutic efficacy of another therapeutic agent.

[0029] A “prophylactically effective amount” of a compound is an amount sufficient to prevent a disease or disorder, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease. The term “prophylactically effective amount” can encompass an amount

that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

4.2 COMPOUNDS

[0030] Provided herein are isotopically enriched compounds, including isotopically enriched pomalidomide, synthetic intermediates thereof, and metabolites thereof.

[0031] Isotopic enrichment (*e.g.*, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. (*See, e.g.*, Lijinsky *et. al.*, Food Cosmet. Toxicol., 20: 393 (1982); Lijinsky *et. al.*, J. Nat. Cancer Inst., 69: 1127 (1982); Mangold *et. al.*, Mutation Res. 308: 33 (1994); Gordon *et. al.*, Drug Metab. Dispos., 15: 589 (1987); Zello *et. al.*, Metabolism, 43: 487 (1994); Gately *et. al.*, J. Nucl. Med., 27: 388 (1986); Wade D, Chem. Biol. Interact. 117: 191 (1999)).

[0032] Without being limited by a particular theory, isotopic enrichment of a drug can be used, for example, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[0033] Replacement of an atom for one of its isotopes may often result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C–H bond is broken during a rate-determining step in a chemical reaction (*i.e.* the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). (*See, e.g,* Foster *et al.*, Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner *et al.*, Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999)).

[0034] The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C–H bond is broken, and the same reaction where

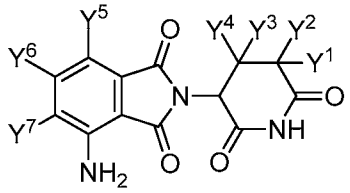
deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. Without being limited by a particular theory, high DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon.

[0035] Tritium ("T") is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T_2O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium ("T") for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ^{13}C or ^{14}C for carbon, ^{33}S, ^{34}S, or ^{36}S for sulfur, ^{15}N for nitrogen, and ^{17}O or ^{18}O for oxygen, may lead to a similar kinetic isotope effect.

[0036] The animal body expresses a variety of enzymes for the purpose of eliminating foreign substances, such as therapeutic agents, from its circulation system. Examples of such enzymes include the cytochrome P450 enzymes ("CYPs"), esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C–H) bond to either a carbon-oxygen (C–O) or carbon-carbon (C–C) pi-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For many drugs, such oxidations are rapid. These drugs therefore often require the administration of multiple or high daily doses.

[0037] Therefore, isotopic enrichment at certain positions of a compound provided herein may produce a detectable KIE that affects the pharmacokinetic, pharmacologic, and/or toxicological profiles of a compound provided herein in comparison with a similar compound having a natural isotopic composition. In one embodiment, the deuterium enrichment is performed on the site of C-H bond cleavage during metabolism.

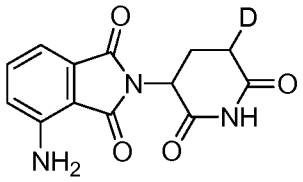
[0038] In some embodiments, provided herein are deuterated analogues of pomalidomide, or pharmaceutically acceptable salt or stereoisomer thereof, in which one or more atomic positions of the pomalidomide molecule, or pharmaceutically acceptable salt or stereoisomer thereof, is/are isotopically enriched with deuterium. Certain embodiments herein provide compounds of the following chemical structure:



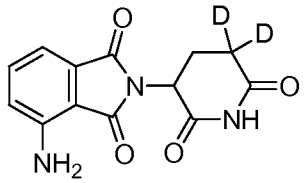
Compound I,

in which one or more Y atoms (*i.e.*, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7) is/are hydrogen(s) isotopically enriched with deuterium, and any remaining Y atom(s) is/are non-enriched hydrogen atom(s). In particular embodiments, one, two, three, four, five, six or seven of the indicated Y atoms is/are isotopically enriched with deuterium, and any remaining Y atom(s) is/are non-enriched hydrogen(s).

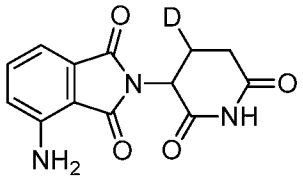
[0039] In certain embodiments, one or more Y atoms on the glutarimide portion of Compound I are deuterium-enriched. For example, particular compounds provided herein include the following listed compounds, in which the label "D" indicates a deuterium-enriched atomic position, *i.e.*, a sample comprising the given compound has a deuterium enrichment at the indicated position(s) above the natural abundance of deuterium:



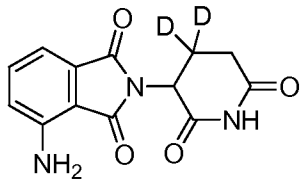
Compound II



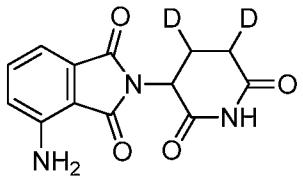
Compound III



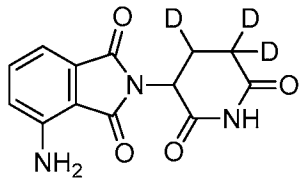
Compound IV



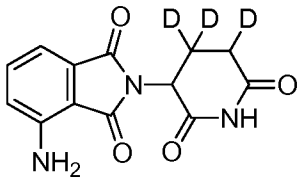
Compound V



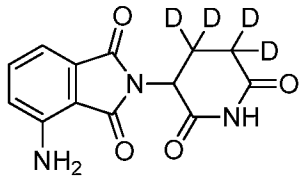
Compound VI



Compound VII

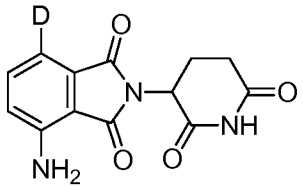


Compound VIII

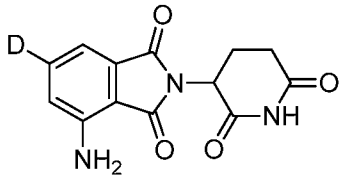


Compound IX

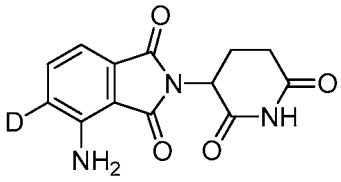
[0040] In certain embodiments, one or more Y atoms on the dioxoisoindoline portion of Compound I are deuterium-enriched. For example, particular compounds provided herein include, but are not limited to, the following listed compounds, in which the label "D" indicates a deuterium-enriched atomic position, *i.e.*, a sample comprising the given compound has a deuterium enrichment at the indicated position(s) above the natural abundance of deuterium:



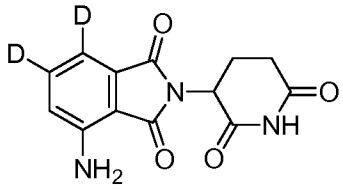
Compound X



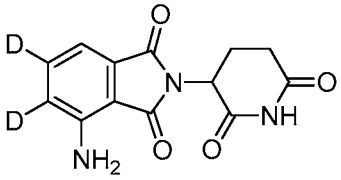
Compound XI



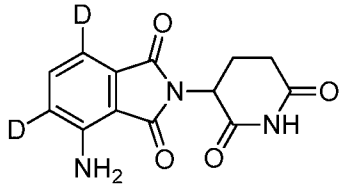
Compound XII



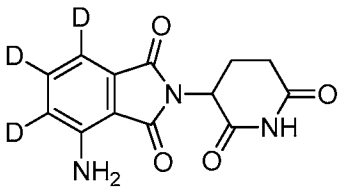
Compound XIII



Compound XIV



Compound XV

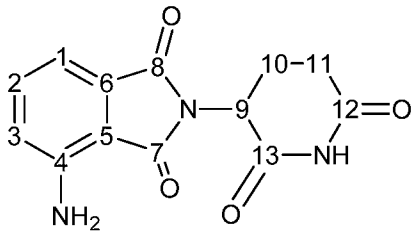


Compound XVI

[0041] In certain embodiments, one or more Y atoms on both the glutarimide portion and the dioxoisoindoline portion of Compound I are deuterium-enriched, *i.e.*, any combination of deuteration shown above for the glutarimide portion and the oxoisoindoline portion is encompassed.

[0042] It is understood that one or more deuteriums may exchange with hydrogen under physiological conditions.

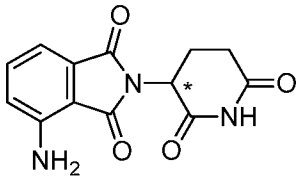
[0043] In some embodiments, provided herein are carbon-13 analogues of pomalidomide, or pharmaceutically acceptable salt or stereoisomer thereof, in which on or more atomic positions of the pomalidomide molecule, or pharmaceutically acceptable salt or stereoisomer thereof, is isotopically enriched with carbon-13. In certain embodiments, provided herein are compounds of the following chemical structure:



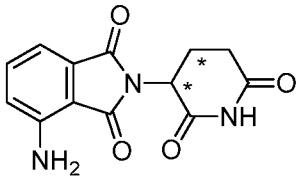
Compound XVII

in which one or more of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 is/are carbon atom(s) isotopically enriched with carbon-13, and any remaining carbon atom(s) is/are non-enriched carbon atom(s). In particular embodiments, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, or thirteen of carbon atom(s) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 is are/isotopically enriched with carbon-13, and any remaining carbon atom(s) is/are non-enriched.

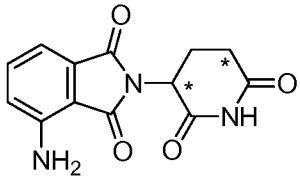
[0044] In certain embodiments, one or more carbon atom(s) of the glutarimide portion of Compound XVII, *i.e.* 9, 10, 11, 12, or 13, is/are carbon-13-enriched. For example, particular compounds provided herein include, but are not limited to, the following compounds, in which the asterisk -*- indicates a carbon-13 enriched atomic position, *i.e.*, a sample comprising the given compound has a carbon-13 enrichment at the indicated position(s) above the nature abundance of carbon-13.



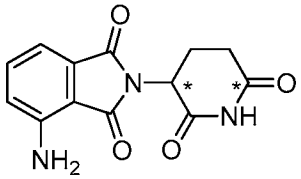
Compound XVIII



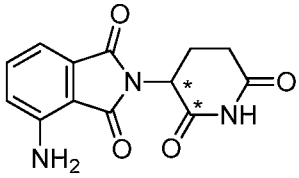
Compound XIX



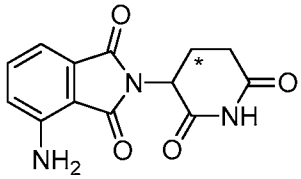
Compound XX



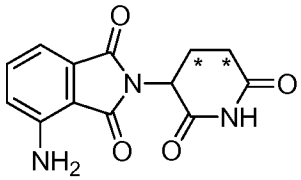
Compound XXI



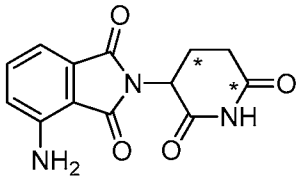
Compound XXII



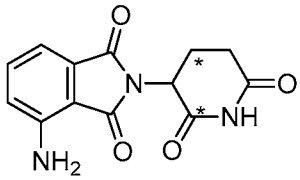
Compound XXIII



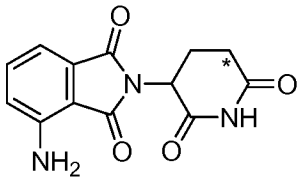
Compound XXIV



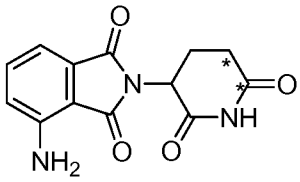
Compound XXV



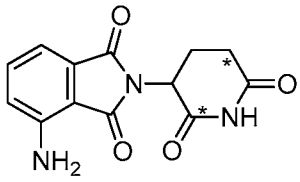
Compound XXVI



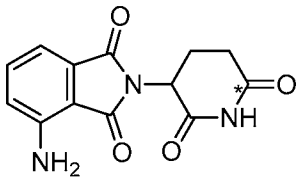
Compound XXVII



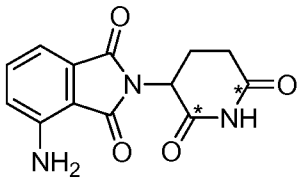
Compound XXVIII



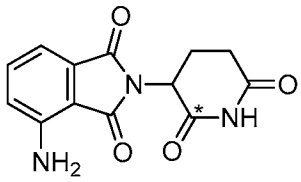
Compound XXIX



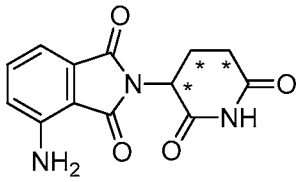
Compound XXX



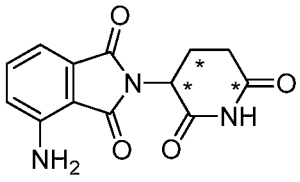
Compound XXXI



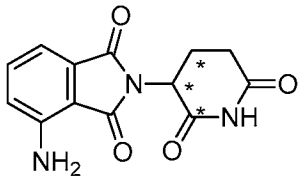
Compound XXXII



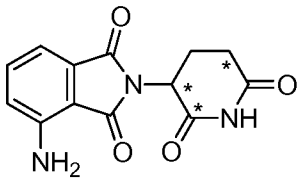
Compound XXXIII



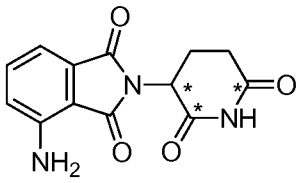
Compound XXXIV



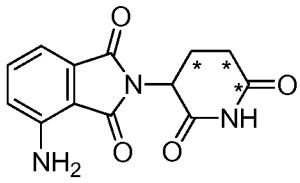
Compound XXXV



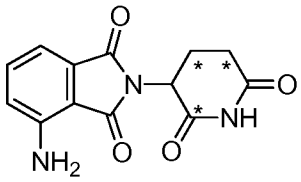
Compound XXXVI



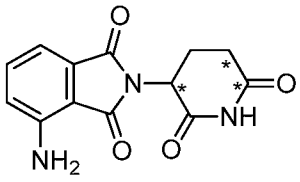
Compound XXXVII



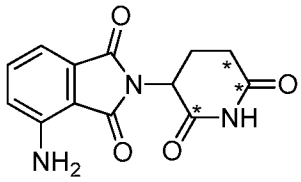
Compound XXXVIII



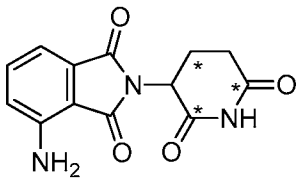
Compound XXXIX



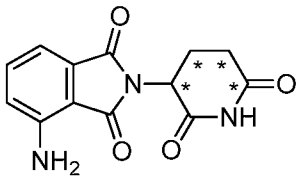
Compound XL



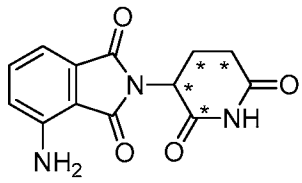
Compound XLI



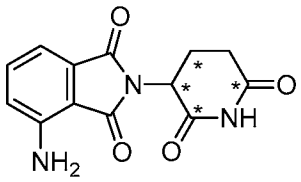
Compound XLII



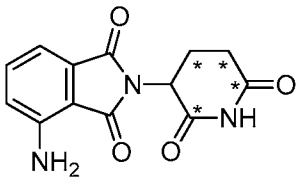
Compound XLIII



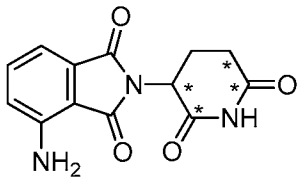
Compound XLIV



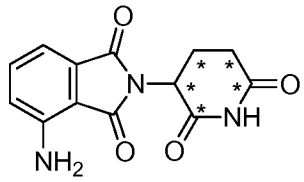
Compound XLV



Compound XLVI



Compound XLVII



Compound XLVIII

[0045] In certain embodiments, one or more carbon atom(s) on the dioxoisoindoline portion of Compound XVII, *i.e.*, 1, 2, 3, 4, 5, 6, 7, or 8, is/are carbon-13-enriched. For example, particular compounds of Compound XVII provided herein are carbon-13 enriched at the following carbon atoms: 1; 2; 3; 4; 5; 6; 7; 8; 1 and 2; 1 and 3; 1 and 4; 1 and 5; 1 and 6; 1 and 7; 1 and 8; 2 and 3; 2 and 4; 2 and 5; 2 and 6; 2 and 7; 2 and 8; 3 and 4; 3 and 5; 3 and 6; 3 and 7; 3 and 8; 4 and 5; 4 and 6; 4 and 7; 4 and 8; 5 and 6; 5 and 7; 5 and 8; 6 and 7; 6 and 8; or 7 and 8.

[0046] In some embodiments, compounds of Compound XVII provided herein are carbon-13 enriched at the following carbon atoms: 1, 2, and 3; 1, 2, and 4; 1, 2, and 5; 1, 2, and 6; 1, 2, and 7; 1, 2, and 8; 1, 3, and 4; 1, 3, and 5; 1, 3, and 6; 1, 3, and 7; 1, 3, and 8; 1, 4, and 5; 1, 4, and 6; 1, 4, and 7; 1, 4, and 8; 1, 5, and 6; 1, 5, and 7; 1, 5, and 8; 1, 6, and 7; 1, 6, and 8; 1, 7, and 8; 2, 3, and 4; 2, 3, and 5; 2, 3, and 6; 2, 3, and 7; 2, 3, and 8; 2, 4, and 5; 2, 4, and 6; 2, 4, and 7; 2, 4, and 8; 2, 5, and 6; 2, 5, and 7; 2, 5, and 8; 2, 6, and 7; 2, 6, and 8; 2, 7, and 8; 3, 4, and 5; 3, 4, and 6; 3, 4, and 7; 3, 4, and 8; 3, 5, and 6; 3, 5, and 7; 3, 5, and 8; 3, 6, and 7; 3, 6, and 8; 3, 7, and 8; 4, 5, and 6; 4, 5, and 7; 4, 5, and 8; 4, 6, and 7; 4, 6, and 8; 4, 7, and 8; 5, 6, and 7; 5, 6, and 8; 5, 7, and 8; or 6, 7, and 8.

[0047] In some embodiments, compounds of Compound XVII provided herein are carbon-13 enriched at the following carbon atoms: 1, 2, 3, and 4; 1, 2, 3, and 5; 1, 2, 3, and 6; 1, 2, 3, and 7; 1, 2, 3, and 8; 1, 2, 4, and 5; 1, 2, 4, and 6; 1, 2, 4, and 7; 1, 2, 4, and 8; 1, 2, 5, and 6; 1, 2, 5, and 7; 1, 2, 5, and 8; 1, 2, 6, and 7; 1, 2, 6, and 8; 1, 2, 7, and 8; 1, 3, 4, and 5; 1, 3, 4, and 6; 1, 3, 4, and 7; 1, 3, 4, and 8; 1, 3, 5, and 6; 1, 3, 5, and 7; 1, 3, 5, and 8; 1, 3, 6, and 7; 1, 3, 6, and 8; 1, 3, 7, and 8; 1, 4, 5, and 6; 1, 4, 5, and 7; 1, 4, 5, and 8; 1, 4, 6, and 7; 1, 4, 6, and 8; 1, 4, 7, and 8; 1, 5, 6, and 7; 1, 5, 6, and 8; 1, 5, 7, and 8; 1, 6, 7, and 8; 2, 3, 4, and 5; 2, 3, 4, and 6; 2, 3, 4, and 7; 2, 3, 4, and 8; 2, 3, 5, and 6; 2, 3, 5, and 7; 2, 3, 5, and 8; 2, 3, 6, and 7; 2, 3, 6, and 8; 2, 3, 7, and 8; 2, 4, 5, and 6; 2, 4, 5, and 7; 2, 4, 5, and 8; 2, 4, 6, and 7; 2, 4, 6, and 8; 2, 4, 7, and 8; 2, 5, 6, and 7; 2, 5, 6, and 8; 2, 5, 7, and 8; 2, 6, 7, and 8; 3, 4, 5, and 6; 3, 4, 5,

and 7; 3, 4, 5, and 8; 3, 4, 6, and 7; 3, 4, 6, and 8; 3, 4, 7, and 8; 3, 5, 6, and 7; 3, 5, 6, and 8; 3, 5, 7, and 8; 3, 6, 7, and 8; 4, 5, 6, and 7; 4, 5, 6, and 8; 4, 5, 7, and 8; 4, 6, 7, and 8; or 5, 6, 7, and 8.

[0048] In some embodiments, compounds of Compound XVII provided herein are carbon-13 enriched at the following carbon atoms: 1, 2, 3, 4, and 5; 1, 2, 3, 4, and 6; 1, 2, 3, 4, and 7; 1, 2, 3, 4, and 8; 1, 2, 3, 5, and 6; 1, 2, 3, 5, and 7; 1, 2, 3, 5, and 8; 1, 2, 3, 6, and 7; 1, 2, 3, 6, and 8; 1, 2, 3, 7, and 8; 1, 2, 4, 5, and 6; 1,2,4,5, and 7; 1, 2, 4, 5, and 8; 1, 2, 4, 6, and 7; 1, 2, 4, 6, and 8; 1, 2, 4, 7, and 8; 1, 2, 5, 6, and 7; 1, 2, 5, 6, and 8; 1, 2, 5, 7, and 8; 1, 2, 6, 7, and 8; 1, 3, 4, 5, and 6; 1, 3, 4, 5, and 7; 1, 3, 4, 5, and 8; 1, 3, 4, 6, and 7; 1, 3, 4, 6, and 8; 1, 3, 4, 7, and 8; 1, 3, 5, 6, and 7; 1, 3, 5, 6, and 8; 1, 3, 5, 7, and 8; 1, 3, 6, 7, and 8; 1, 4, 5, 6, and 7; 1, 4, 5, 6, and 8; 1, 4, 5, 7, and 8; 1, 4, 6, 7, and 8; 1, 5, 6, 7, and 8; 2, 3, 4, 5, and 6; 2, 3, 4, 5, and 7; 2, 3, 4, 5, and 8; 2, 3, 4, 6, and 7; 2, 3, 4, 6, and 8; 2, 3, 4, 7, and 8; 2, 3, 5, 6, and 7; 2, 3, 5, 6, and 8; 2, 3, 5, 7, and 8; 2, 3, 6, 7, and 8; 2, 4, 5, 6, and 7; 2, 4, 5, 6, and 8; 2, 4, 5, 7, and 8; 2, 4, 6, 7, and 8; 2, 5, 6, 7, and 8; 3, 4, 5, 6, and 7; 3, 4, 5, 6, and 8; 3, 4, 5, 7, and 8; 3, 4, 6, 7, and 8; 3, 5, 6, 7, and 8; or 4, 5, 6, 7, and 8.

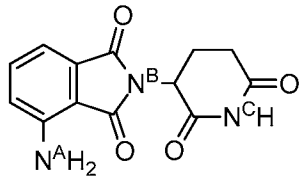
[0049] In some embodiments, compounds of Compound XVII provided herein are carbon-13 enriched at the following carbon atoms: 1, 2, 3, 4, 5, and 6; 1, 2, 3, 4, 5, and 7; 1, 2, 3, 4, 5, and 8; 1, 2, 3, 4, 6, and 7; 1, 2, 3, 4, 6, and 8; 1, 2, 3, 4, 7, and 8; 1, 2, 3, 5, 6, and 7; 1, 2, 3, 5, 6, and 8; 1, 2, 3, 6, 7, and 8; 1, 2, 4, 5, 6, and 7; 1, 2, 4, 5, 6, and 8; 1, 2, 4, 5, 7, and 8; 1, 2, 5, 6, 7, and 8; 1, 3, 4, 5, 6, and 7; 1, 3, 4, 5, 6, and 8; 1, 3, 4, 5, 7, and 8; 1, 3, 4, 6, 7, and 8; 1, 3, 5, 6, 7, and 8; 1, 4, 5, 6, 7, and 8; 2, 3, 4, 5, 6, and 7; 2, 3, 4, 5, 6, and 8; 2, 3, 4, 5, 7, and 8; 2, 3, 4, 6, 7, and 8; 2, 3, 5, 6, 7, and 8; 2, 4, 5, 6, 7, and 8; or 3, 4, 5, 6, 7, and 8.

[0050] In some embodiments, compounds of Compound XVII provided herein are carbon-13 enriched at the following carbon atoms: 1, 2, 3, 4, 5, 6, and 7; 1, 2, 3, 4, 5, 6, and 8; 1, 2, 3, 4, 5, 7, and 8; 1, 2, 3, 4, 6, 7, and 8; 1, 2, 3, 5, 6, 7, and 8; 1, 2, 4, 5, 6, 7, and 8; 1, 3, 4, 5, 6, 7, and 8; 2, 3, 4, 5, 6, 7, and 8; or 1, 2, 3, 4, 5, 6, 7, and 8.

[0051] In certain embodiments, one or more carbon atoms on both the glutarimide portion and the oxoisoindoline portion of Compound XVII are carbon-13-enriched, *i.e.*, any combination of isotopically-enriched positions shown above for the glutarimide portion and the oxoisoindoline portion is encompassed.

[0052] In some embodiments, provided herein are nitrogen-15 analogues of pomalidomide, or pharmaceutically acceptable salt or stereoisomer thereof, in which one

or more atomic positions of the pomalidomide molecule, or pharmaceutically acceptable salt or stereoisomer thereof, is isotopically enriched with nitrogen 15. In certain embodiments, provided herein are compounds of the following chemical structure:



Compound XLIX

in which one or more of nitrogen atom(s) N^A, N^B, or N^C is/are isotopically enriched with nitrogen-15, and any remaining nitrogen atom(s) is/are non-enriched nitrogen atom(s). In particular embodiments, one, two, or three of N^A, N^B, or N^C is/are isotopically enriched with nitrogen-15, and any remaining nitrogen atom(s) is/are non-enriched.

[0053] In certain embodiments, N^A is enriched with nitrogen-15. In certain embodiments, N^B is enriched with nitrogen-15. In certain embodiments, N^C is enriched with nitrogen-15. In certain embodiments, N^A and N^B are both enriched with nitrogen-15. In certain embodiments, N^A and N^C are both enriched with nitrogen-15. In certain embodiments, N^B and N^C are both enriched with nitrogen-15. In certain embodiments, N^A, N^B and N^C are all enriched with nitrogen-15

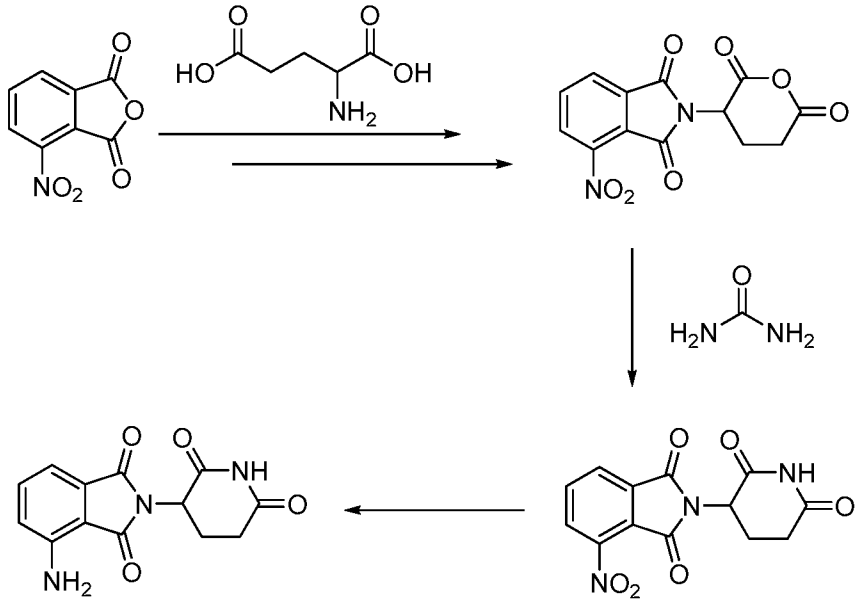
[0054] In certain embodiments, one or more hydrogen(s) is/are enriched with deuterium(s) and one or more carbon(s) is/are enriched with carbon-13. In certain embodiments, one or more hydrogen(s) is/are enriched with deuterium and one or more nitrogen(s) is/are enriched with nitrogen-15. In certain embodiments, one or more carbon atom(s) is/are enriched with carbon-13 and one or more nitrogen(s) is/are enriched with nitrogen-15. In certain embodiments, one or more hydrogen(s) is/are enriched with deuterium, one or more carbon(s) are enriched with carbon-13, and one or more nitrogen(s) is/are replaced with nitrogen-15.

4.2.1 SYNTHESIS

[0055] The compounds described herein may be synthesized using methods known to those of ordinary skill in the art. In some embodiments, synthetic organic chemistry techniques are utilized. In certain embodiments, isotopic enrichment of pomalidomide is accomplished through the use of isotopically-enriched reagents. In certain embodiments, the synthesis of isotopically-enriched pomalidomide may be accomplished based on the known synthetic routes to chemically synthesize

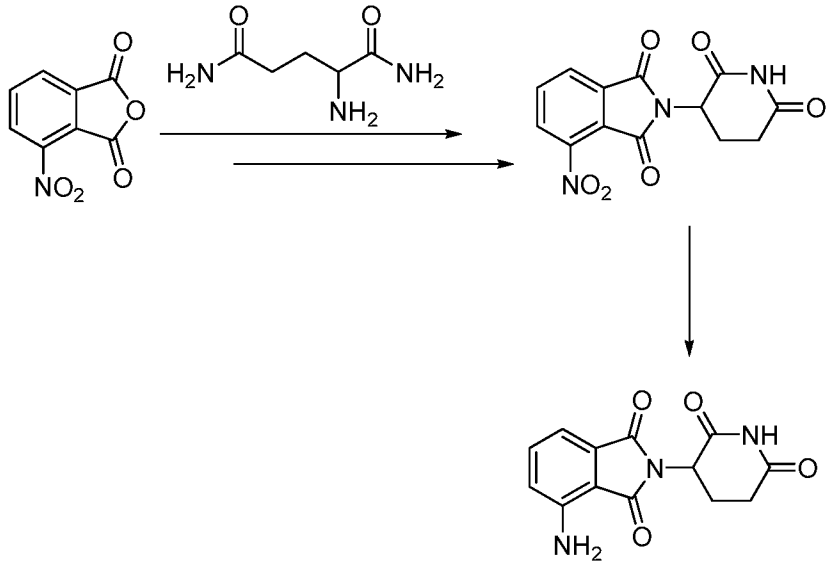
pomalidomide, wherein one or more of the reagents, starting materials, precursors, and/or intermediates of the synthetic routes are replaced with one or more isotopically-enriched reagents, starting materials, precursors, and/or intermediates. Such isotopically-enriched reagents, starting materials, precursors, and intermediates may be purchased commercially or made synthetically using methods known in the art. In some embodiments, isotopically-enriched pomalidomide may be synthesized based on the synthetic methods described in U.S. Patent Number 5,635,517, which is incorporated herein by reference in its entirety.

[0056] In some embodiments, pomalidomide may be enriched with deuterium, ^{13}C, and/or ^{15}N via the following scheme:



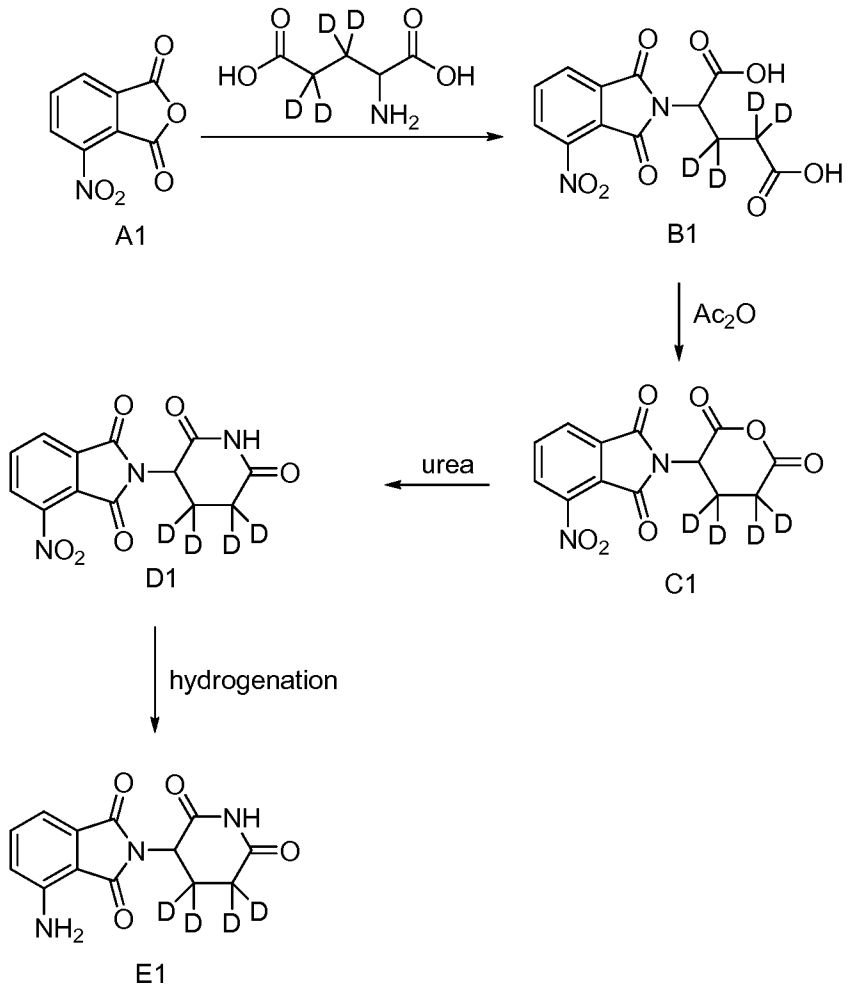
wherein the starting materials, reagents, and/or intermediates are isotopcially-enriched.

[0057] In some embodiments, pomalidomide may be enriched with deuterium, ^{13}C, and/or ^{15}N via the following scheme below:



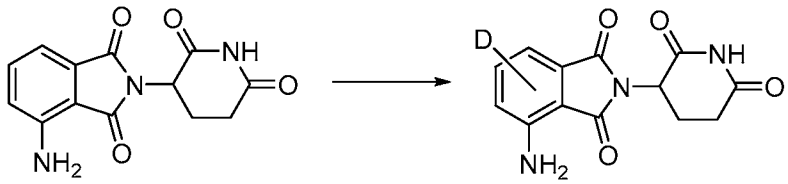
wherein the starting materials, reagents, and/or intermediates are isotopcially-enriched.

[0058] In certain embodiments, the glutarimide portion of pomalidomide may be enriched with deuterium and/or ^{13}C using deuterium- and/or ^{13}C- enriched glutamic acid. For example, commercially available deuterated glutamic acid may be reacted with Compound A1 to form Compound B1. Compound B1 may be subsequently transformed into Compound C1 in the presence of acetic anhydride. Compound C1 may then be transformed into Compound D1 via reaction with urea. Deuterated pomalidomide may be obtained from Compound D1 via hydrogenation.



[0059] ^{13}C-enrichment of the glutaramide ring may be obtained in a similar fashion by utilizing ^{13}C-labeled glutamic acid.

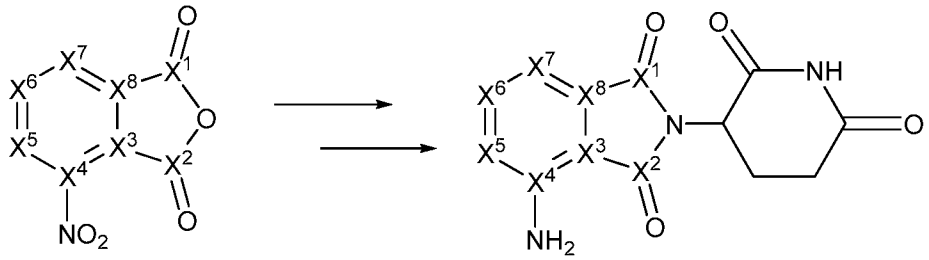
[0060] In some embodiments, one or more hydrogen positions of the insoindoline portion are enriched with deuterium. In certain embodiments, this is accomplished by directly subjecting pomalidomide to reaction conditions suitable for the deuteration of the aromatic ring as shown in the following reaction scheme.



[0061] Such conditions are known to those of ordinary skill in the art including, for example, those disclosed in the following references, each of which are incorporated herein by reference in their entireties: U.S. Publication No. 2007/0255076; March, J. "Advanced Organic Chemistry, Reactions, Mechanisms, and Structure," Fourth Ed., Wiley, New York, 1992; Larsen *et al.*, *J. Org. Chem.*, 43, 18, 1978; Blake *et al.*, *J. Chem. Soc., Chem Commun.*, 1975, 930; and references cited therein. In certain

embodiments, pomalidomide is first converted into a pomalidomide derivative that is suitable for aromatic deuteration, this derivative is subjected to aromatic deuteration conditions, and the so-obtained deuterated pomalidomide derivative is converted to deuterated pomalidomide.

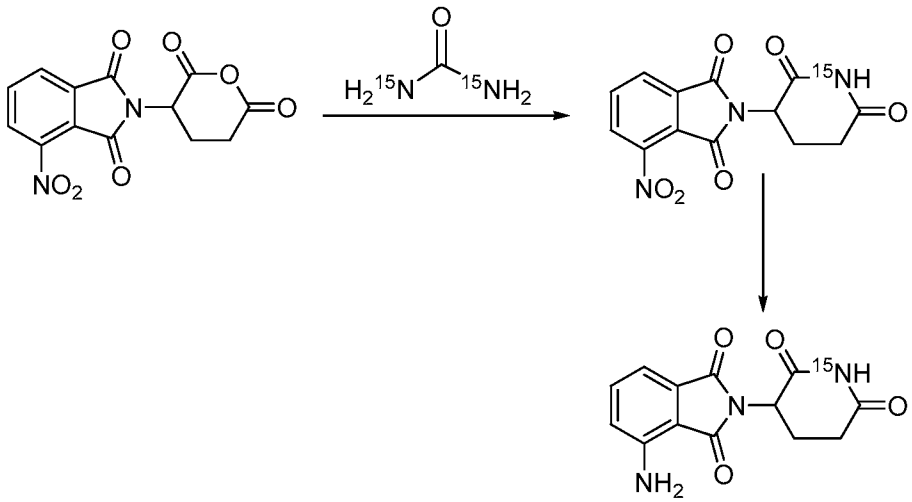
[0062] In certain embodiments, the isoindoline portion of pomalidomide may be enriched with ^{13}C by utilizing Compound A2, wherein X^1-X^8 are each, independently, ^{13}C or C, using methods similar to those described above.



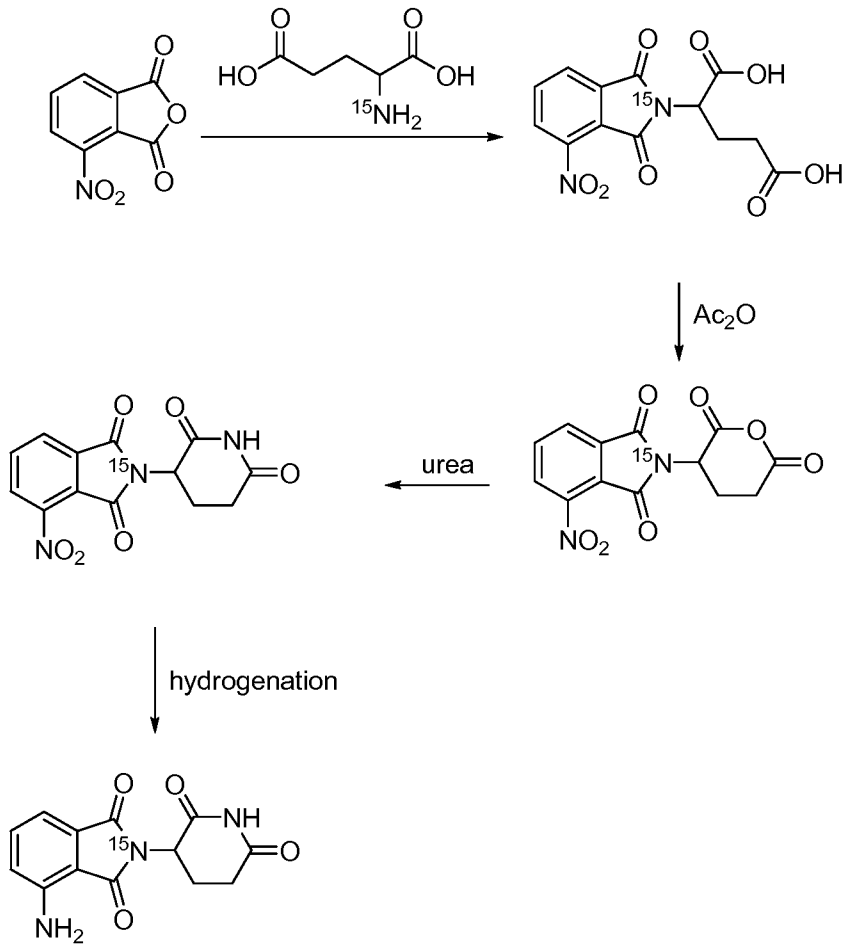
A2

[0063] In certain embodiments, the amino group of the insoindoline portion of pomalidomide may be enriched with ^{15}N by utilizing ^{15}N enriched 4-nitroisobenzofuran-1,3, dione, wherein the nitro group is enriched with ^{15}N, in the synthesis route described above.

[0064] In certain embodiments, ^{15}N-enriched pomalidomide may be synthesized via the following sequence.



[0065] In certain embodiments, ^{15}N-enriched pomalidomide may be synthesized via the following sequence.



[0066] It will be apparent to those of ordinary skill in the art that certain combinations of the above methods may be used to isotopically enrich multiple positions of pomalidomide.

4.3 METHODS OF TREATMENT, PREVENTION AND MANAGEMENT

[0067] Provided herein are methods of treating, preventing, and/or managing various diseases or disorders using a compound provided herein, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), prodrug, clathrate, or stereoisomer thereof. Without being limited by a particular theory, compounds provided herein can control angiogenesis or inhibit the production of certain cytokines including, but not limited to, TNF-α, IL-1β, IL-12, IL-18, GM-CSF, and/or IL-6. Without being limited by a particular theory, compounds provided herein can stimulate the production of certain other cytokines including IL-10, and also act as a costimulatory signal for T cell activation, resulting in increased production of cytokines such as, but not limited to, IL-12 and/or IFN-γ. In addition, compounds provided herein can enhance the effects of NK cells and antibody-mediated cellular cytotoxicity (ADCC). Further, compounds

provided herein may be immunomodulatory and/or cytotoxic, and thus, may be useful as chemotherapeutic agents. Consequently, without being limited by a particular theory, some or all of such characteristics possessed by the compounds provided herein may render them useful in treating, managing, and/or preventing various diseases or disorders.

[0068] Examples of diseases or disorders include, but are not limited to, cancer, disorders associated with angiogenesis, pain including, but not limited to, Complex Regional Pain Syndrome ("CRPS"), Macular Degeneration ("MD") and related syndromes, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases, immunodeficiency disorders, CNS disorders, CNS injury, atherosclerosis and related disorders, dysfunctional sleep and related disorders, hemoglobinopathy and related disorders (*e.g.*, anemia), TNFα related disorders, and other various diseases and disorders.

[0069] Examples of cancer and precancerous conditions include, but are not limited to, those described in U.S. patent nos. 6,281,230 and 5,635,517 to Muller *et al.*, in various U.S. patent publications to Zeldis, including publication nos. 2004/0220144A1, published November 4, 2004 (Treatment of Myelodysplastic Syndrome); 2004/0029832A1, published February 12, 2004 (Treatment of Various Types of Cancer); and 2004/0087546, published May 6, 2004 (Treatment of Myeloproliferative Diseases). Examples also include those described in WO 2004/103274, published December 2, 2004. All of these references are incorporated herein in their entireties by reference.

[0070] Specific examples of cancer include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The compounds are also useful for treating cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias. The compounds provided herein can be used for treating, preventing or managing either primary or metastatic tumors.

[0071] Other specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma,

anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, metastatic melanoma (localized melanoma, including, but not limited to, ocular melanoma), malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation.

[0072] In one embodiment, provided herein are methods of treating, preventing or managing various forms of leukemias such as chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia and acute myeloblastic leukemia, including leukemias that are relapsed, refractory or resistant, as disclosed in U.S. publication no. 2006/0030594, published February 9, 2006, which is incorporated in its entirety by reference.

[0073] The term "leukemia" refers malignant neoplasms of the blood-forming tissues. The leukemia includes, but is not limited to, chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia and acute myeloblastic leukemia. The leukemia can be relapsed, refractory or resistant to conventional therapy. The term "relapsed" refers to a situation where patients who have had a remission of leukemia after therapy have a return of leukemia cells in the marrow and a decrease in normal blood cells. The term "refractory or resistant" refers to a circumstance where patients, even after intensive treatment, have residual leukemia cells in their marrow.

[0074] In another embodiment, provided herein are methods of treating, preventing or managing various types of lymphomas, including Non-Hodgkin's lymphoma (NHL). The term "lymphoma" refers a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. "NHL" refers to malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal tract. Examples of NHL include, but are not limited to, mantle cell lymphoma (MCL), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma (ILL), diffuse poorly differentiated lymphocytic lymphoma (PDL), centrocytic lymphoma, diffuse small-cleaved cell lymphoma (DSCCL), follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma).

[0075] Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle). Specific examples of the diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, arthritis, endometriosis, Crohn's disease, heart failure, advanced heart failure, renal impairment, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, and 5q-deletion syndrome.

[0076] Examples of pain include, but are not limited to those described in U.S. patent publication no. 2005/0203142, published September 15, 2005, which is incorporated herein by reference. Specific types of pain include, but are not limited to, nociceptive pain, neuropathic pain, mixed pain of nociceptive and neuropathic pain, visceral pain, migraine, headache and post-operative pain.

[0077] Examples of nociceptive pain include, but are not limited to, pain associated with chemical or thermal burns, cuts of the skin, contusions of the skin, osteoarthritis, rheumatoid arthritis, tendonitis, and myofascial pain.

[0078] Examples of neuropathic pain include, but are not limited to, CRPS type I, CRPS type II, reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy,

reflex dystrophy, sympathetically maintained pain syndrome, causalgia, Sudeck atrophy of bone, algoneurodystrophy, shoulder hand syndrome, post-traumatic dystrophy, trigeminal neuralgia, post herpetic neuralgia, cancer related pain, phantom limb pain, fibromyalgia, chronic fatigue syndrome, spinal cord injury pain, central post-stroke pain, radiculopathy, diabetic neuropathy, post-stroke pain, luetic neuropathy, and other painful neuropathic conditions such as those induced by drugs such as vincristine and velcade.

[0079] As used herein, the terms "complex regional pain syndrome," "CRPS" and "CRPS and related syndromes" mean a chronic pain disorder characterized by one or more of the following: pain, whether spontaneous or evoked, including allodynia (painful response to a stimulus that is not usually painful) and hyperalgesia (exaggerated response to a stimulus that is usually only mildly painful); pain that is disproportionate to the inciting event (*e.g.*, years of severe pain after an ankle sprain); regional pain that is not limited to a single peripheral nerve distribution; and autonomic dysregulation (*e.g.*, edema, alteration in blood flow and hyperhidrosis) associated with trophic skin changes (hair and nail growth abnormalities and cutaneous ulceration).

[0080] Examples of MD and related syndromes include, but are not limited to, those described in U.S. patent publication no. 2004/0091455, published May 13, 2004, which is incorporated herein by reference. Specific examples include, but are not limited to, atrophic (dry) MD, exudative (wet) MD, age-related maculopathy (ARM), choroidal neovascularization (CNVM), retinal pigment epithelium detachment (PED), and atrophy of retinal pigment epithelium (RPE).

[0081] Examples of skin diseases include, but are not limited to, those described in U.S. publication no. 2005/0214328A1, published September 29, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, keratoses and related symptoms, skin diseases or disorders characterized with overgrowths of the epidermis, acne, and wrinkles.

[0082] As used herein, the term "keratosis" refers to any lesion on the epidermis marked by the presence of circumscribed overgrowths of the horny layer, including but not limited to actinic keratosis, seborrheic keratosis, keratoacanthoma, keratosis follicularis (Darier disease), inverted follicular keratosis, palmoplantar keratoderma (PPK, keratosis palmaris et plantaris), keratosis pilaris, and stucco keratosis. The term "actinic keratosis" also refers to senile keratosis, keratosis senilis, verruca senilis, plana senilis, solar keratosis, keratoderma or keratoma. The term "seborrheic keratosis" also refers to seborrheic wart, senile wart, or basal cell papilloma.

Keratosis is characterized by one or more of the following symptoms: rough appearing, scaly, erythematous papules, plaques, spicules or nodules on exposed surfaces (*e.g.*, face, hands, ears, neck , legs and thorax), excrescences of keratin referred to as cutaneous horns, hyperkeratosis, telangiectasias, elastosis, pigmented lentigines, acanthosis, parakeratosis, dyskeratoses, papillomatosis, hyperpigmentation of the basal cells, cellular atypia, mitotic figures, abnormal cell-cell adhesion, dense inflammatory infiltrates and small prevalence of squamous cell carcinomas.

[0083] Examples of skin diseases or disorders characterized with overgrowths of the epidermis include, but are not limited to, any conditions, diseases or disorders marked by the presence of overgrowths of the epidermis, including but not limited to, infections associated with papilloma virus, arsenical keratoses, sign of Leser-Trélat, warty dyskeratoma (WD), trichostasis spinulosa (TS), erythrokeratodermia variabilis (EKV), ichthyosis fetalis (harlequin ichthyosis), knuckle pads, cutaneous melanoacanthoma, porokeratosis, psoriasis, squamous cell carcinoma, confluent and reticulated papillomatosis (CRP), acrochordons, cutaneous horn, cowden disease (multiple hamartoma syndrome), dermatosis papulosa nigra (DPN), epidermal nevus syndrome (ENS), ichthyosis vulgaris, molluscum contagiosum, prurigo nodularis, and acanthosis nigricans (AN).

[0084] Examples of pulmonary disorders include, but are not limited to, those described in U.S. publication no. 2005/0239842A1, published October 27, 2005, which is incorporated herein by reference. Specific examples include pulmonary hypertension and related disorders. Examples of pulmonary hypertension and related disorders include, but are not limited to: primary pulmonary hypertension (PPH); secondary pulmonary hypertension (SPH); familial PPH; sporadic PPH; precapillary pulmonary hypertension; pulmonary arterial hypertension (PAH); pulmonary artery hypertension; idiopathic pulmonary hypertension; thrombotic pulmonary arteriopathy (TPA); plexogenic pulmonary arteriopathy; functional classes I to IV pulmonary hypertension; and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vasular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure

to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus including systemic and cutaneous lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

[0085] Examples of asbestos-related disorders include, but not limited to, those described in U.S. publication no. 2005/0100529, published May 12, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, mesothelioma, asbestosis, malignant pleural effusion, benign exudative effusion, pleural plaques, pleural calcification, diffuse pleural thickening, rounded atelectasis, fibrotic masses, and lung cancer.

[0086] Examples of parasitic diseases include, but are not limited to, those described in U.S. publication no. 2006/0154880, published July 13, 2006, which is incorporated herein by reference. Parasitic diseases include diseases and disorders caused by human intracellular parasites such as, but not limited to, *P. falcifarium*, *P. ovale*, *P. vivax*, *P. malariae*, *L. donovari*, *L. infantum*, *L. aethiopica*, *L. major*, *L. tropica*, *L. mexicana*, *L. braziliensis*, *T. Gondii*, *B. microti*, *B. divergens*, *B. coli*, *C. parvum*, *C. cayetanensis*, *E. histolytica*, *I. belli*, *S. mansonii*, *S. haematobium*, *Trypanosoma ssp.*, *Toxoplasma ssp.*, and *O. volvulus*. Other diseases and disorders caused by non-human intracellular parasites such as, but not limited to, *Babesia bovis*, *Babesia canis*, *Banesia Gibsoni*, *Besnoitia darlingi*, *Cytauxzoon felis*, *Eimeria ssp.*, *Hammondia ssp.*, and *Theileria ssp.*, are also encompassed. Specific examples include, but are not limited to, malaria, babesiosis, trypanosomiasis, leishmaniasis, toxoplasmosis, meningoencephalitis, keratitis, amebiasis, giardiasis, cryptosporidiosis, isosporiasis, cyclosporiasis, microsporidiosis, ascariasis, trichuriasis, ancylostomiasis, strongyloidiasis, toxocariasis, trichinosis, lymphatic filariasis, onchocerciasis, filariasis, schistosomiasis, and dermatitis caused by animal schistosomes.

[0087] Examples of immunodeficiency disorders include, but are not limited to, those described in U.S. publication no. 2006/0188475, published August 24, 2006. Specific examples include, but not limited to, adenosine deaminase deficiency, antibody deficiency with normal or elevated Igs, ataxia-tenlangiectasia, bare lymphocyte syndrome, common variable immunodeficiency, Ig deficiency with hyper-IgM, Ig heavy chain deletions, IgA deficiency, immunodeficiency with thymoma, reticular dysgenesis, Nezelof syndrome, selective IgG subclass deficiency, transient hypogammaglobulinemia

of infancy, Wistcott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked severe combined immunodeficiency.

[0088] Examples of CNS disorders include, but are not limited to, those described in U.S. publication no. 2005/0143344, published June 30, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, include, but are not limited to, Amyotrophic Lateral Sclerosis, Alzheimer Disease, Parkinson Disease, Huntington's Disease, Multiple Sclerosis other neuroimmunological disorders such as Tourette Syndrome, delerium, or disturbances in consciousness that occur over a short period of time, and amnestic disorder, or discreet memory impairments that occur in the absence of other central nervous system impairments.

[0089] Examples of CNS injuries and related syndromes include, but are not limited to, those described in U.S. publication no. 2006/0122228, published June 8, 2006, which is incorporated herein by reference. Specific examples include, but are not limited to, CNS injury/damage and related syndromes, include, but are not limited to, primary brain injury, secondary brain injury, traumatic brain injury, focal brain injury, diffuse axonal injury, head injury, concussion, post-concussion syndrome, cerebral contusion and laceration, subdural hematoma, epidermal hematoma, post-traumatic epilepsy, chronic vegetative state, complete SCI, incomplete SCI, acute SCI, subacute SCI, chronic SCI, central cord syndrome, Brown-Sequard syndrome, anterior cord syndrome, conus medullaris syndrome, cauda equina syndrome, neurogenic shock, spinal shock, altered level of consciousness, headache, nausea, emesis, memory loss, dizziness, diplopia, blurred vision, emotional lability, sleep disturbances, irritability, inability to concentrate, nervousness, behavioral impairment, cognitive deficit, and seizure.

[0090] Other disease or disorders include, but not limited to, viral, genetic, allergic, and autoimmune diseases. Specific examples include, but not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft versus host disease, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythrematosus, ENL in leprosy, radiation damage, cancer, asthma, or hyperoxic alveolar injury.

[0091] Examples of atherosclerosis and related conditions include, but are not limited to, those disclosed in U.S. publication no. 2002/0054899, published May 9, 2002, which is incorporated herein by reference. Specific examples include, but are not limited to, all forms of conditions involving atherosclerosis, including restenosis after vascular intervention such as angioplasty, stenting, atherectomy and grafting. All forms of vascular intervention are contemplated herein, including diseases of the cardiovascular and renal system, such as, but not limited to, renal angioplasty, percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA), carotid percutaneous transluminal angioplasty (PTA), coronary by-pass grafting, angioplasty with stent implantation, peripheral percutaneous transluminal intervention of the iliac, femoral or popliteal arteries, and surgical intervention using impregnated artificial grafts. The following chart provides a listing of the major systemic arteries that may be in need of treatment, all of which are contemplated herein:

Artery	Body Areas Supplied
Axillary	Shoulder and axilla
Brachial	Upper arm
Brachiocephalic	Head, neck, and arm
Celiac	Divides into left gastric, splenic, and hepatic arteries
Common carotid	Neck
Common iliac	Divides into external and internal iliac arteries
Coronary	Heart
Deep femoral	Thigh
Digital	Fingers
Dorsalis pedis	Foot
External carotid	Neck and external head regions
External iliac	Femoral artery
Femoral	Thigh
Gastric	Stomach
Hepatic	Liver, gallbladder, pancreas, and duodenum
Inferior mesenteric	Descending colon, rectum, and pelvic wall
Internal carotid	Neck and internal head regions
Internal iliac	Rectum, urinary bladder, external genitalia, buttocks muscles, uterus and vagina
Left gastric	Esophagus and stomach
Middle sacral	Sacrum
Ovarian	Ovaries
Palmar arch	Hand
Peroneal	Calf
Popliteal	Knee
Posterior tibial	Calf
Pulmonary	Lungs
Radial	Forearm
Renal	Kidney
Splenic	Stomach, pancreas, and spleen
Subclavian	Shoulder
Superior mesenteric	Pancreas, small intestine, ascending and transverse colon
Testicular	Testes
Ulnar	Forearm

[0092] Examples of dysfunctional sleep and related syndromes include, but are not limited to, those disclosed in U.S. publication no. 2005/0222209A1, published October 6, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, snoring, sleep apnea, insomnia, narcolepsy, restless leg syndrome, sleep terrors, sleep walking sleep eating, and dysfunctional sleep associated with chronic neurological or inflammatory conditions. Chronic neurological or inflammatory conditions, include, but are not limited to, Complex Regional Pain Syndrome, chronic low back pain, musculoskeletal pain, arthritis, radiculopathy, pain associated with cancer, fibromyalgia, chronic fatigue syndrome, visceral pain, bladder pain, chronic pancreatitis, neuropathies (diabetic, post-herpetic, traumatic or inflammatory), and neurodegenerative disorders such as Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's Disease, bradykinesia; muscle rigidity; parkinsonian tremor; parkinsonian gait; motion freezing; depression; defective long-term memory, Rubinstein-Taybi syndrome (RTS); dementia; postural instability; hypokinetic disorders; synuclein disorders; multiple system atrophies; striatonigral degeneration; olivopontocerebellar atrophy; Shy-Drager syndrome; motor neuron disease with parkinsonian features; Lewy body dementia; Tau pathology disorders; progressive supranuclear palsy; corticobasal degeneration; frontotemporal dementia; amyloid pathology disorders; mild cognitive impairment; Alzheimer disease with parkinsonism; Wilson disease; Hallervorden-Spatz disease; Chediak-Hagashi disease; SCA-3 spinocerebellar ataxia; X-linked dystonia parkinsonism; prion disease; hyperkinetic disorders; chorea; ballismus; dystonia tremors; Amyotrophic Lateral Sclerosis (ALS); CNS trauma and myoclonus.

[0093] Examples of hemoglobinopathy and related disorders include, but are not limited to, those described in U.S. publication no. 2005/0143420A1, published June 30, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, hemoglobinopathy, sickle cell anemia, and any other disorders related to the differentiation of CD34+ cells.

[0094] Examples of TNFα related disorders include, but are not limited to, those described in WO 98/03502 and WO 98/54170, both of which are incorporated herein in their entireties by reference. Specific examples include, but are not limited to: endotoxemia or toxic shock syndrome; cachexia; adult respiratory distress syndrome; bone resorption diseases such as arthritis; hypercalcemia; Graft versus Host Reaction; cerebral malaria; inflammation; tumor growth; chronic pulmonary inflammatory

diseases; reperfusion injury; myocardial infarction; stroke; circulatory shock; rheumatoid arthritis; Crohn's disease; HIV infection and AIDS; other disorders such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis and other arthritic conditions, septic shock, septis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythromatosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS; disorders such as septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, oncogenic or cancerous conditions, asthma, autoimmune disease, radiation damages, and hyperoxic alveolar injury; viral infections, such as those caused by the herpes viruses; viral conjunctivitis; or atopic dermatitis.

[0095] In other embodiments, the use of compounds provided herein in various immunological applications, in particular, as vaccine adjuvants, particularly anticancer vaccine adjuvants, as disclosed in U.S. publication no. 2007/0048327, published March 1, 2007, which is incorporated herein in its entirety by reference, is also encompassed. These embodiments also relate to the uses of compounds provided herein in combination with vaccines to treat or prevent cancer or infectious diseases, and other various uses of immunomodulatory compounds such as reduction or desensitization of allergic reactions.

[0096] Doses of a compound provided herein, or a pharmaceutically acceptable salt, solvate, clathrate, stereoisomer or prodrug thereof, vary depending on factors such as: specific indication to be treated, prevented, or managed; age and condition of a patient; and amount of second active agent used, if any. Generally, a compound provided herein, or a pharmaceutically acceptable salt, solvate, clathrate, stereoisomer or prodrug thereof, may be used in an amount of from about 0.1 mg to about 500 mg per day, and can be adjusted in a conventional fashion (*e.g.*, the same amount administered each day of the treatment, prevention or management period), in cycles (*e.g.*, one week on, one week off), or in an amount that increases or decreases over the course of treatment, prevention, or management. In other embodiments, the dose can be from about 1 mg to about 300 mg, from about 0.1 mg to about 150 mg, from about 1 mg to about 200 mg, from about 10 mg to about 100 mg, from about 0.1 mg to about 50 mg, from about 1 mg to about 50 mg, from about 10 mg to about 50 mg, from about 20 mg to about 30 mg, or from about 1 mg to about 20 mg.

4.4 SECOND ACTIVE AGENTS

[0097] A compound provided herein, or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof, can be combined with other pharmacologically active compounds ("second active agents") in methods and compositions provided herein. Certain combinations may work synergistically in the treatment of particular types diseases or disorders, and conditions and symptoms associated with such diseases or disorders. A compound provided herein, or a pharmaceutically acceptable salt, solvate, clathrate, stereoisomer or prodrug thereof, can also work to alleviate adverse effects associated with certain second active agents, and *vice versa*.

[0098] One or more second active ingredients or agents can be used in the methods and compositions provided herein. Second active agents can be large molecules (*e.g.*, proteins) or small molecules (*e.g.*, synthetic inorganic, organometallic, or organic molecules).

[0099] Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies. Specific examples of the active agents are anti-CD40 monoclonal antibodies (such as, for example, SGN-40); histone deacetlyase inhibitors (such as, for example, SAHA and LAQ 824); heat-shock protein-90 inhibitors (such as, for example, 17-AAG); insulin-like growth factor-1 receptor kinase inhibitors; vascular endothelial growth factor receptor kinase inhibitors (such as, for example, PTK787); insulin growth factor receptor inhibitors; lysophosphatidic acid acyltransrerase inhibitors; IkB kinase inhibitors; p38MAPK inhibitors; EGFR inhibitors (such as, for example, gefitinib and erlotinib HCL); HER-2 antibodies (such as, for example, trastuzumab (Herceptin®) and pertuzumab (Omnitarg™)); VEGFR antibodies (such as, for example, bevacizumab (Avastin™)); VEGFR inhibitors (such as, for example, flk-1 specific kinase inhibitors, SU5416 and ptk787/zk222584); P13K inhibitors (such as, for example, wortmannin); C-Met inhibitors (such as, for example, PHA-665752); monoclonal antibodies (such as, for example, rituximab (Rituxan®), tositumomab (Bexxar®), edrecolomab (Panorex®) and G250); and anti-TNF-α antibodies. Examples of small molecule active agents include, but are not limited to, anticancer agents and antibiotics (*e.g.*, clarithromycin).

[00100] Specific second active compounds that can be combined with compounds provided herein vary depending on the specific indication to be treated, prevented or managed.

[00101] For instance, for the treatment, prevention or management of cancer, second active agents include, but are not limited to: semaxanib; cyclosporin; etanercept; doxycycline; bortezomib; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin;

sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

[00102] Other second agents include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine;

edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imatinib (Gleevec®), imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (Genasense®); O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine

hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[00103] Specific second active agents include, but are not limited to, 2-methoxyestradiol, telomestatin, inducers of apoptosis in mutiple myeloma cells (such as, for example, TRAIL), statins, semaxanib, cyclosporin, etanercept, doxycycline, bortezomib, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatinum, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (*e.g.*, PEG INTRON-A),

capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

[00104] In another embodiment, examples of specific second agents according to the indications to be treated, prevented, or managed can be found in the following references, all of which are incorporated herein in their entireties: U.S. patent nos. 6,281,230 and 5,635,517; U.S. publication nos. 2004/0220144, 2004/0190609, 2004/0087546, 2005/0203142, 2004/0091455, 2005/0100529, 2005/0214328, 2005/0239842, 2006/0154880, 2006/0122228,and 2005/0143344; and U.S. provisional application no. 60/631,870.

[00105] Examples of second active agents that may be used for the treatment, prevention and/or management of pain include, but are not limited to, conventional therapeutics used to treat or prevent pain such as antidepressants, anticonvulsants, antihypertensives, anxiolytics, calcium channel blockers, muscle relaxants, non-narcotic analgesics, opioid analgesics, anti-inflammatories, cox-2 inhibitors, immunomodulatory agents, alpha-adrenergic receptor agonists or antagonists, immunosuppressive agents, corticosteroids, hyperbaric oxygen, ketamine, other anesthetic agents, NMDA antagonists, and other therapeutics found, for example, in the *Physician's Desk Reference* 2003. Specific examples include, but are not limited to, salicylic acid acetate (Aspirin®), celecoxib (Celebrex®), Enbrel®, ketamine, gabapentin (Neurontin®), phenytoin (Dilantin®), carbamazepine (Tegretol®), oxcarbazepine (Trileptal®), valproic acid (Depakene®), morphine sulfate, hydromorphone, prednisone, griseofulvin, penthonium, alendronate, dyphenhydramide, guanethidine, ketorolac (Acular®), thyrocalcitonin, dimethylsulfoxide (DMSO), clonidine (Catapress®), bretylium, ketanserin, reserpine, droperidol, atropine, phentolamine, bupivacaine, lidocaine, acetaminophen, nortriptyline (Pamelor®), amitriptyline (Elavil®), imipramine (Tofranil®), doxepin (Sinequan®), clomipramine (Anafranil®), fluoxetine (Prozac®), sertraline (Zoloft®), naproxen, nefazodone (Serzone®), venlafaxine (Effexor®), trazodone (Desyrel®), bupropion (Wellbutrin®), mexiletine, nifedipine, propranolol, tramadol, lamotrigine, vioxx, ziconotide, ketamine, dextromethorphan, benzodiazepines, baclofen, tizanidine and phenoxybenzamine.

[00106] Examples of second active agents that may be used for the treatment, prevention and/or management of macular degeneration and related syndromes include, but are not limited to, a steroid, a light sensitizer, an integrin, an antioxidant, an interferon, a xanthine derivative, a growth hormone, a neutrotrophic factor, a regulator of neovascularization, an anti-VEGF antibody, a prostaglandin, an antibiotic, a phytoestrogen, an anti-inflammatory compound or an antiangiogenesis compound, or a combination thereof. Specific examples include, but are not limited to, verteporfin, purlytin, an angiostatic steroid, rhuFab, interferon-2α, pentoxifylline, tin etiopurpurin, motexafin, lucentis, lutetium, 9-fluoro-11,21-dihydroxy-16, 17-1-methylethylidinebis(oxy)pregna-1,4-diene-3,20-dione, latanoprost (see U.S. Patent No. 6,225,348), tetracycline and its derivatives, rifamycin and its derivatives, macrolides, metronidazole (U.S. Patent Nos. 6,218,369 and 6,015,803), genistein, genistin, 6'-O-Mal genistin, 6'-O-Ac genistin, daidzein, daidzin, 6'-O-Mal daidzin, 6'-O-Ac daidzin, glycitein, glycitin, 6'-O-Mal glycitin, biochanin A, formononetin (U.S. Patent No. 6,001,368), triamcinolone acetomide, dexamethasone (U.S. Patent No. 5,770,589), thalidomide, glutathione (U.S. Patent No. 5,632,984), basic fibroblast growth factor (bFGF), transforming growth factor b (TGF-b), brain-derived neurotrophic factor (BDNF), plasminogen activator factor type 2 (PAI-2), EYE101 (Eyetech Pharmaceuticals), LY333531 (Eli Lilly), Miravant, and RETISERT implant (Bausch & Lomb). All of the references cited herein are incorporated in their entireties by reference.

[00107] Examples of second active agents that may be used for the treatment, prevention and/or management of skin diseases include, but are not limited to, keratolytics, retinoids, α-hydroxy acids, antibiotics, collagen, botulinum toxin, interferon, steroids, and immunomodulatory agents. Specific examples include, but are not limited to, 5-fluorouracil, masoprocol, trichloroacetic acid, salicylic acid, lactic acid, ammonium lactate, urea, tretinoin, isotretinoin, antibiotics, collagen, botulinum toxin, interferon, corticosteroid, transretinoic acid and collagens such as human placental collagen, animal placental collagen, Dermalogen, AlloDerm, Fascia, Cymetra, Autologen, Zyderm, Zyplast, Resoplast, and Isolagen.

[00108] Examples of second active agents that may be used for the treatment, prevention and/or management of pulmonary hepertension and related disorders include, but are not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelin antagonists,

phosphodiesterase inhibitors (e.g., PDE V inhibitors), endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors, and other therapeutics known to reduce pulmonary artery pressure. Specific examples include, but are not limited to, warfarin (Coumadin®), a diuretic, a cardiac glycoside, digoxin-oxygen, diltiazem, nifedipine, a vasodilator such as prostacyclin (*e.g.*, prostaglandin I2 (PGI2), epoprostenol (EPO, Floran®), treprostinil (Remodulin®), nitric oxide (NO), bosentan (Tracleer®), amlodipine, epoprostenol (Floran®), treprostinil (Remodulin®), prostacyclin, tadalafil (Cialis®), simvastatin (Zocor®), omapatrilat (Vanlev®), irbesartan (Avapro®), pravastatin (Pravachol®), digoxin, L-arginine, iloprost, betaprost, and sildenafil (Viagra®).

[00109] Examples of second active agents that may be used for the treatment, prevention and/or management of asbestos-related disorders include, but are not limited to, anthracycline, platinum, alkylating agent, oblimersen (Genasense®), cisplatinum, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, taxotere, irinotecan, capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, bleomycin, hyaluronidase, mitomycin C, mepacrine, thiotepa, tetracycline and gemcitabine.

[00110] Examples of second active agents that may be used for the treatment, prevention and/or management of parasitic diseases include, but are not limited to, chloroquine, quinine, quinidine, pyrimethamine, sulfadiazine, doxycycline, clindamycin, mefloquine, halofantrine, primaquine, hydroxychloroquine, proguanil, atovaquone, azithromycin, suramin, pentamidine, melarsoprol, nifurtimox, benznidazole, amphotericin B, pentavalent antimony compounds (*e.g.*, sodium stiboglucuronate), interfereon gamma, itraconazole, a combination of dead promastigotes and BCG, leucovorin, corticosteroids, sulfonamide, spiramycin, IgG (serology), trimethoprim, and sulfamethoxazole.

[00111] Examples of second active agents that may be used for the treatment, prevention and/or management of immunodeficiency disorders include, but are not limited to: antibiotics (therapeutic or prophylactic) such as, but not limited to, ampicillin, tetracycline, penicillin, cephalosporins, streptomycin, kanamycin, and erythromycin; antivirals such as, but not limited to, amantadine, rimantadine, acyclovir, and ribavirin; immunoglobulin; plasma; immunologic enhancing drugs such as, but not limited to,

levami sole and isoprinosine; biologics such as, but not limited to, gammaglobulin, transfer factor, interleukins, and interferons; hormones such as, but not limited to, thymic; and other immunologic agents such as, but not limited to, B cell stimulators (*e.g.*, BAFF/BlyS), cytokines (e.g., IL-2, IL-4, and IL-5), growth factors (*e.g.*, TGF-α), antibodies (*e.g.*, anti-CD40 and IgM), oligonucleotides containing unmethylated CpG motifs, and vaccines (*e.g.*, viral and tumor peptide vaccines).

[00112] Examples of second active agents that may be used for the treatment, prevention and/or management of CNS disorders include, but are not limited to: opioids; a dopamine agonist or antagonist, such as, but not limited to, Levodopa, L-DOPA, cocaine, α-methyl-tyrosine, reserpine, tetrabenazine, benzotropine, pargyline, fenodolpam mesylate, cabergoline, pramipexole dihydrochloride, ropinorole, amantadine hydrochloride, selegiline hydrochloride, carbidopa, pergolide mesylate, Sinemet CR, and Symmetrel; a MAO inhibitor, such as, but not limited to, iproniazid, clorgyline, phenelzine and isocarboxazid; a COMT inhibitor, such as, but not limited to, tolcapone and entacapone; a cholinesterase inhibitor, such as, but not limited to, physostigmine saliclate, physostigmine sulfate, physostigmine bromide, meostigmine bromide, neostigmine methylsulfate, ambenonim chloride, edrophonium chloride, tacrine, pralidoxime chloride, obidoxime chloride, trimedoxime bromide, diacetyl monoxim, endrophonium, pyridostigmine, and demecarium; an anti-inflammatory agent, such as, but not limited to, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, Rho-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone and benzbromarone or betamethasone and other glucocorticoids; and an antiemetic agent, such as, but not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine,

dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and a mixture thereof.

[00113] Examples of second active agents that may be used for the treatment, prevention and/or management of CNS injuries and related syndromes include, but are not limited to, immunomodulatory agents, immunosuppressive agents, antihypertensives, anticonvulsants, fibrinolytic agents, antiplatelet agents, antipsychotics, antidepressants, benzodiazepines, buspirone, amantadine, and other known or conventional agents used in patients with CNS injury/damage and related syndromes. Specific examples include, but are not limited to: steroids (*e.g.*, glucocorticoids, such as, but not limited to, methylprednisolone, dexamethasone and betamethasone); an anti-inflammatory agent, including, but not limited to, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, RHo-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone and benzbromarone; a cAMP analog including, but not limited to, db-cAMP; an agent comprising a methylphenidate drug, which comprises l-threo-methylphenidate, d-threo-methylphenidate, dl-threo-methylphenidate, l-erythro-methylphenidate, d-erythro-methylphenidate, dl-erythro-methylphenidate, and a mixture thereof; and a diuretic agent such as, but not limited to, mannitol, furosemide, glycerol, and urea.

[00114] Examples of second active agent that may be used for the treatment, prevention and/or management of dysfunctional sleep and related syndromes include, but are not limited to, a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent (gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate), an antiaryhthmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, a second immunomodulatory

compound, a combination agent, and other known or conventional agents used in sleep therapy. Specific examples include, but are not limited to, Neurontin, oxycontin, morphine, topiramate, amitryptiline, nortryptiline, carbamazepine, Levodopa, L-DOPA, cocaine, α-methyl-tyrosine, reserpine, tetrabenazine, benzotropine, pargyline, fenodolpam mesylate, cabergoline, pramipexole dihydrochloride, ropinorole, amantadine hydrochloride, selegiline hydrochloride, carbidopa, pergolide mesylate, Sinemet CR, Symmetrel, iproniazid, clorgyline, phenelzine, isocarboxazid, tolcapone, entacapone, physostigmine saliclate, physostigmine sulfate, physostigmine bromide, meostigmine bromide, neostigmine methylsulfate, ambenonim chloride, edrophonium chloride, tacrine, pralidoxime chloride, obidoxime chloride, trimedoxime bromide, diacetyl monoxim, endrophonium, pyridostigmine, demecarium, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, RHo-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone, benzbromarone, betamethasone and other glucocorticoids, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and a mixture thereof.

[00115] Examples of second active agents that may be used for the treatment, prevention and/or management of hemoglobinopathy and related disorders include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-I a, and interferon gamma-I b; and G-CSF; hydroxyurea; butyrates or butyrate derivatives;

nitrous oxide; hydroxy urea; HEMOXIN™ (NIPRISAN™; *see* United States Patent No. 5,800,819); Gardos channel antagonists such as clotrimazole and triaryl methane derivatives; Deferoxamine; protein C; and transfusions of blood, or of a blood substitute such as Hemospan™ or Hemospan™ PS (Sangart).

[00116] Administration of a compound provided herein, or a pharmaceutically acceptable salt, solvate, clathrate, stereoisomer or prodrug thereof, and the second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. One of administration for compounds provided herein is oral. Routes of administration for the second active agents or ingredients are known to those of ordinary skill in the art. *See*, *e.g.*, *Physicians' Desk Reference* (60^{th} ed., 2006).

[00117] In one embodiment, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of compounds provided herein and any optional additional active agents concurrently administered to the patient.

[00118] As discussed elsewhere herein, also encompassed is a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. Compounds provided herein and other active ingredients can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

4.5 CYCLING THERAPY

[00119] In certain embodiments, the prophylactic or therapeutic agents provided herein are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest (*i.e.*, discontinuation of the administration) for a period of time, and repeating this sequential

administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[00120] Consequently, in one embodiment, a compound provided herein is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. Cycling therapy further allows the frequency, number, and length of dosing cycles to be increased. Thus, another embodiment encompasses the administration of a compound provided herein for more cycles than are typical when it is administered alone. In yet another embodiment, a compound provided herein is administered for a greater number of cycles than would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

[00121] In one embodiment, a compound provided herein is administered daily and continuously for three or four weeks at a dose of from about 0.1 mg to about 500 mg per day, followed by a rest of one or two weeks. In other embodiments, the dose can be from about 1 mg to about 300 mg, from about 0.1 mg to about 150 mg, from about 1 mg to about 200 mg, from about 10 mg to about 100 mg, from about 0.1 mg to about 50 mg, from about 1 mg to about 50 mg, from about 10 mg to about 50 mg, from about 20 mg to about 30 mg, or from about 1 mg to about 20 mg, followed by a rest.

[00122] In one embodiment, a compound provided herein and a second active ingredient are administered orally, with administration of the compound provided herein occurring 30 to 60 minutes prior to the second active ingredient, during a cycle of four to six weeks. In another embodiment, the combination of a compound provided herein and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle.

[00123] Typically, the number of cycles during which the combination treatment is administered to a patient will be from about one to about 24 cycles, from about two to about 16 cycles, or from about four to about three cycles.

4.6 PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[00124] Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms provided herein comprise a compound provided herein, or a pharmaceutically acceptable

salt, solvate, stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms can further comprise one or more excipients.

[00125] Pharmaceutical compositions and dosage forms provided herein can also comprise one or more additional active ingredients. Examples of optional second, or additional, active ingredients are disclosed in Section 4.4, above.

[00126] Single unit dosage forms provided herein are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (*e.g.*, eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[00127] The composition, shape, and type of dosage forms will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms are used will vary from one another will be readily apparent to those skilled in the art. *See*, *e.g.*, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

[00128] In one embodiment, pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a

patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, provided are pharmaceutical compositions and dosage forms that contain little, if any, lactose other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

[00129] Lactose-free compositions can comprise excipients that are well known in the art and are listed, for example, in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. In one embodiment, lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[00130] Also provided are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See*, *e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[00131] Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00132] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous

compositions are, in one embodiment, packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[00133] Also provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[00134] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. In one embodiment, dosage forms comprise a compound provided herein in an amount of from about 0.10 to about 500 mg. In other embodiments, dosage forms comprise a compound provided herein in an amount of about 0.1, 1, 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg.

[00135] In other embodiments, dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the second active agent will depend on the specific agent used, the diseases or disorders being treated or managed, and the amount(s) of a compound provided herein, and any optional additional active agents concurrently administered to the patient.

4.6.1 ORAL DOSAGE FORMS

[00136] Pharmaceutical compositions that are suitable for oral administration can be provided as discrete dosage forms, such as, but not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See generally*, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

[00137] Oral dosage forms provided herein are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For

example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00138] In one embodiment, oral dosage forms are tablets or capsules, in which case solid excipients are employed. In another embodiment, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[00139] For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00140] Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[00141] Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[00142] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms provided herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions is, in one embodiment, present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[00143] Disintegrants may be used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients may be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. In one embodiment, pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, or from about 1 to about 5 weight percent of disintegrant.

[00144] Disintegrants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[00145] Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants may be used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

[00146] In one embodiment, a solid oral dosage form comprises a compound provided herein, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

4.6.2 CONTROLLED RELEASE DOSAGE FORMS

[00147] Active ingredients provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active agents provided herein. In one embodiment, provided are single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[00148] In one embodiment, controlled-release pharmaceutical products improve drug therapy over that achieved by their non-controlled counterparts. In another embodiment, the use of a controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[00149] In another embodiment, the controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an

extended period of time. In one embodiment, in order to maintain a constant level of drug in the body, the drug can be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

4.6.3 PARENTERAL DOSAGE FORMS

[00150] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. In some embodiments, administration of a parenteral dosage form bypasses patients' natural defenses against contaminants, and thus, in these embodiments, parenteral dosage forms are sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[00151] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00152] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms. For example, cyclodextrin and its derivatives can be used to increase the solubility of a compound provided herein. *See, e.g.*, U.S. Patent No. 5,134,127, which is incorporated herein by reference.

4.6.4 TOPICAL AND MUCOSAL DOSAGE FORMS

[00153] Topical and mucosal dosage forms provided herein include, but are not limited to, sprays, aerosols, solutions, emulsions, suspensions, eye drops or other ophthalmic preparations, or other forms known to one of skill in the art. *See*, *e.g.*, *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

[00154] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed herein are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. In one embodiment, excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms. Examples of additional ingredients are well known in the art. *See*, *e.g.*, *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

[00155] The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Also, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In other embodiments, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, or as a delivery-enhancing or penetration-enhancing agent. In other embodiments, salts, solvates, prodrugs, clathrates, or stereoisomers of the active ingredients can be used to further adjust the properties of the resulting composition.

4.7 KITS

[00156] In one embodiment, active ingredients provided herein are not administered to a patient at the same time or by the same route of administration. In

another embodiment, provided are kits which can simplify the administration of appropriate amounts of active ingredients.

[00157] In one embodiment, a kit comprises a dosage form of a compound provided herein. Kits can further comprise additional active ingredients such as oblimersen (Genasense®), melphalan, G-CSF, GM-CSF, EPO, topotecan, dacarbazine, irinotecan, taxotere, IFN, COX-2 inhibitor, pentoxifylline, ciprofloxacin, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, isotretinoin, 13 cis-retinoic acid, or a pharmacologically active mutant or derivative thereof, or a combination thereof. Examples of the additional active ingredients include, but are not limited to, those disclosed herein (*see*, *e.g.*, section 4.3).

[00158] In other embodiments, kits can further comprise devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

[00159] Kits can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5. EXAMPLES

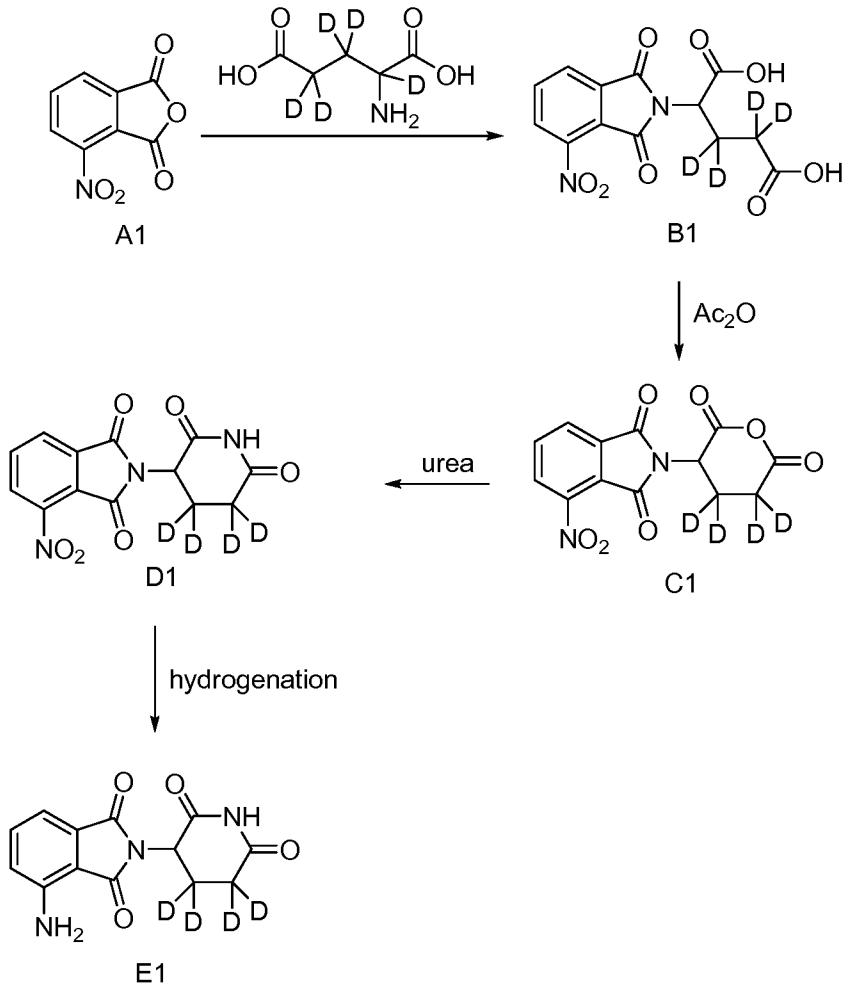
[00160] Isotopically enriched analogs of the compounds provided herein may generally be prepared according known procedures for the synthesis of pomalidomide, wherein one or more of the reagents, starting materials, precursors, or intermediates used is replaced by one or more isotopically enriched reagents, starting materials, precursors, or intermediates. Isotopically enriched reagents, starting materials, precursors, or

intermediates are commercially available or may be prepared by routine procedures known to one of skill in the art. Schemes for the preparation of exemplary isotopically enriched compounds are illustrated below.

5.1 DEUTERATION OF POMALIDOMIDE

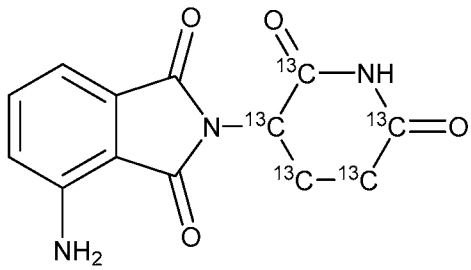
Example 1

[00161] The gluarimide portion of pomalidomide is enriched with deuterium as follows. Anhydride A1 and deuterium-enriched (2,3,3,4,4 –D5) gluatamic acid, which is commercially available, is refluxed in pyridine for about 4 hours and subsequently concentrated to obtain Compound B1. Compound B1 is then mixed in acetic anhydride overnight to obtain Compound C1. Compound C1 is mixed with urea at about 210 °C under nitrogen to obtain Compound D1. Compound D1 is treated with 10% Pd/C in 1,4-dioxane under hydrogen gas (50 psi); the catalyst is filtered off through a celite pad and the filtrate concentrated and purified to obtain deuterated pomalidomide.



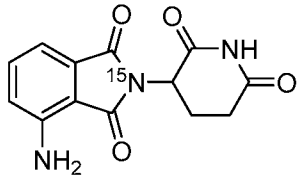
Example 2

[00162] The glutarimide portion of pomalidomide may be enriched with ^{13}C using a procedure similar to Example 1, except that commercially available ^{13}C-enriched glutamic acid is used. This will afford the following compound.



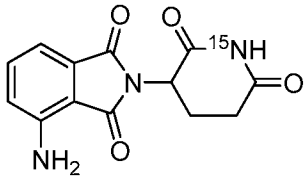
Example 3

[00163] ^{15}N-enriched pomalidomide may be synthesized using a procedure similar to Example 1, except that commercially available ^{15}N-enriched glutamic acid is used. This will afford the following compound.



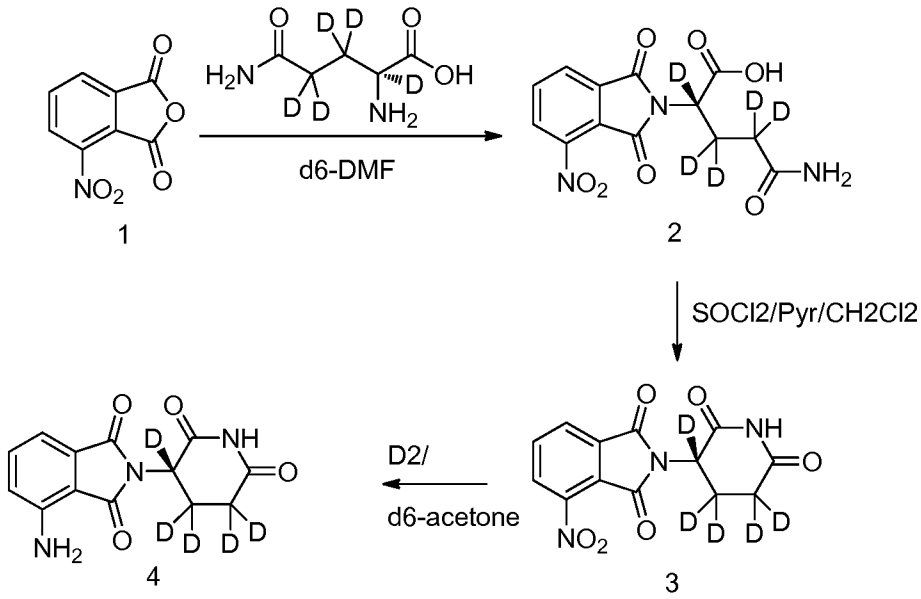
Example 4

[00164] ^{15}N-enriched pomalidomide may be synthesized using a procedure similar to Example 1, except that commercially available ^{15}N-enriched urea is used. This will afford the following compound.



5.2 PREPARATION OF DEUTERATED (S)-POMALIDOMIDE

[00165] The glutarimide portion of S-isomer of pomalidomide is enriched with deuterium as shown in the figure below. Anhydride 1 and deuterium-enriched (2,3,3,4,4 –d5) L-gluatamine (available from Cambridge Isotope Laboratory), is refluxed in d6-DMF to give 2. The Glutarimide group is formed by thionyl chloride assisted coupling at low temperature to afford 3. Reduction of the nitro 3 provides 4. The optical purity can be further enhanced by purification with chiral HPLC. The procedure is according to that in US patent US 799,432,7.



5.2.1 Preparation of (2S)-5-amino-2-(4-nitro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-5-oxo(2H5)pentanoic acid (2)

[00166] A mixture of d6-DMF (37 mL), 3-nitrophthalic anhydride (4.0 g) and (2,3,3,4,4-d5) L-glutamine (3.0 g) is stirred at 80-87 °C for 8 hours. After the reaction is complete, the reaction mixture is allowed to cool to room temperature and then concentrated to an oil under a reduced pressure on a heating bath at 40 °C. The oil is stirred with water to produce a slurry. The slurry is filtered, washed with water, air dried and then dried in a vacuum oven to give (2S)-5-amino-2-(4-nitro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-5-oxo($^2H_5$)pentanoic acid.

5.2.2 Preparation of 2-[(3S)-2,6-dioxo(3,4,4,5,5-2H5)piperidin-3-yl]-4-nitro-1H-isoindole-1,3(2H)-dione (3)

[00167] A suspension mixture of (2S)-5-amino-2-(4-nitro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-5-oxo($^2H_5$)pentanoic acid (4.3 g) in anhydrous methylene chloride (170 mL) is cooled to -40 °C. Thionyl chloride (1.03 mL) is added dropwise followed by pyridine (1.17 mL). After 30 minutes, triethylamine (2.06 mL) is added and the mixture is stirred at -30 to -40 °C. The mixture is filtered and wished with methylene chloride to yield a solid. The solid is recrystallized from acetone (300 mL) to yield 2-[(3S)-2,6-dioxo(3,4,4,5,5-$^2H_5$)piperidin-3-yl]-4-nitro-1H-isoindole-1,3(2H)-dione.

5.2.3 Preparation of 4-amino-2-[(3S)-2,6-dioxo(3,4,4,5,5-2H5)piperidin-3-yl]-1H-isoindole-1,3(2H)-dione (4)

[00168] A mixture of 2-[(3S)-2,6-dioxo(3,4,4,5,5-2H5)piperidin-3-yl]-4-nitro-1H-isoindole-1,3(2H)-dione and 10% Pd/C (0.3 g) in d6-acetone (200 mL) is hydrogenated in a Parr-Shaker apparatus at 50 psi of deuterium gas for 24 hours. The mixture is filtered through celite and the filtrate is concentrated in vacuo. The solid is stirred with hot ethyl acetate to give 4-amino-2-[(3S)-2,6-dioxo(3,4,4,5,5-2H5)piperidin-3-yl]-1H-isoindole-1,3(2H)-dione. The title compound is purified by chiral HPLC: Daicel Chiral Pak AD, 30/70 Hexane/IPA R-isomer 9.55 min and S-isomer12.55 min; to give 4-amino-2-[(3S)-2,6-dioxo(3,4,4,5,5-$^{2}H_5$)piperidin-3-yl]-1H-isoindole-1,3(2H)-dione (4).

5.3 DETERMINATION OF ISOTOPIC ENRICHMENT

[00169] Isotopic enrichment may be confirmed may be confirmed and quantified by mass spectrometry and/or NMR, including, for example, proton-NMR; carbon-13 NMR; or nitrogen-15 NMR.

[00170] Isotopic enirichment may also be confirmed by single-crystal neutron diffraction. For example, the isotopic ratio at a particular hydrogen/deuterium position in a deuterated pomalidomide compound can be determined using single-crystal neutron diffraction. Neutron diffraction is advantageous because neutrons are scattered by the nucleus of an atom, therefore allowing for discrimination between isotopes, such as hydrogen and deuterium, that differ in the number of neutrons in the nucleus.

[00171] A single crystal of suitable size and quality comprising the deuterated pomalidomide compound is grown using standard methods of crystal growth. For single-crystal neutron diffraction experiments, crystals of several cubic millimeters are generally required for suitable data collection. A minimum size for a single crystal is typically about 1 cubic millimeter. Suitable single crystals are obtained by dissolving the deuterated pomalidomide compound in a solvent with appreciable solubility, then slowly evaporating or cooling the solution to yield crystals of suitable size and quality. Alternatively, suitable single crystals are obtained by dissolving the deuterated pomalidomide compound in a solvent with appreciable solubility, then slowly diffusing into the solution of antisolvent (*i.e.*, a solvent in which the deuterated pomalidomide compound is not appreciably soluble) to yield crystals of suitable size and quality. These and other suitable methods of crystal growth are known in the art and are

described, *e.g.*, in George H. Stout & Lyle H. Jensen, X-Ray Structure Determination: A Practical Guide 74-92 (John Wiley & Sons, Inc. 2nd ed. 1989) (the entirety of which is incorporated herein).

[00172] After isolating a suitable single crystal comprising the deuterated pomalidomide compound, the crystal is mounted in a neutron beam, neutron diffraction data is collected, and the crystal structure is solved and refined. Different neutron sources can be used, including steady-state sources and pulsed spallation sources. Examples of steady-state sources include the Grenoble ILL High Flux Reactor (Grenoble, France) and the Oak Ridge High Flux Isotope Reactor (Oak Ridge, Tennessee). Examples of pulsed spallation sources include ISIS, the spallation neutron source at Rutherford Appleton Laboratory (Oxfordshire, UK); the Intense Pulsed Neutron Source (IPNS) at Argonne National Laboratory (Argonne, Illinois), the Los Alamos Neutron Science Center (LANSCE) at Los Alamos National Laboratory (Los Alamos, New Mexico), and the Neutron Science Laboratory (KENS) at KEK (Tsukuba, Ibaraki, Japan).

[00173] For a steady-state neutron source, four-circle diffractometer techniques are used with a monochromatic beam and a single detector, rotating the crystal and detector to measure each reflection sequentially. Diffractometer control software and step-scanning methods for intensity extraction can be adopted from routine four-circle X-ray diffractometry methods. One or more area detectors, including area detector arrays, may alternatively be used to increase the region of reciprocal space accessed in a single measurement. A broad band (white) beam used with an area detector allows for Laue or quasi-Laue diffraction with a stationary crystal and detector.

[00174] For a pulse source with a white neutron beam, time-of-flight Laue diffraction techniques are used, which allow for the determination of the velocity, energy, and wavelength of each neutron detected. This approach combines wavelength sorting with large area position-sensitive detectors, and allows for fixed scattering geometries (*i.e.*, a stationary crystal and detector). Pulse source data collected in this fashion allows for rapid collection of data sets and good accuracy and precision in standard structural refinements. Additional details regarding steady-state and pulse source neutron diffraction experiments are well known in the art. *See, e.g.*, Chick C. Wilson, *Neutron Single Crystal Diffraction*, 220 Z. Kristallogr. 385-98 (2005) (incorporated by reference herein in its entirety).

[00175] Crystal structure data, including particular isotopic ratios, are obtained from neutron diffraction data following routine structure solution and refinement processes. Structure solution is carried out using one of several methods, including direct methods and Patterson methods. For convenience, atomic coordinates from prior single crystal X-ray diffraction experiments may be used as a starting point for structure refinement using neutron diffraction data; this approach permits additional refinement of atomic positions, including hydrogen and deuterium positions. Refinement is conducted using full-matrix least-squares methods to achieve optimal agreement between the observed diffraction intensities and those calculated from the structural model. Ideally, full anisotropic refinement is carried out on all atoms, including the H/D atomic positions of interest. Data collection, structure solution and structure refinement methods, both for X-ray and neutron diffraction data, are well known in the art. *See, e.g.*, Chick C. Wilson, Single Crystal Neutron Diffraction from Molecular Materials (World Scientific Publishing Co. 2000); George H. Stout & Lyle H. Jensen, X-Ray Structure Determination: A Practical Guide (John Wiley & Sons, Inc. 2nd ed. 1989) (both of which are incorporated herein in their entireties).

[00176] The isotopic ratio for a particular position on a deuterated pomalidomide compound is calculated by examining the neutron scattering cross sections for the H/D atomic position of interest. The scattering cross section is obtained as part of the refinement process discussed above. An example of determining the isotopic ratio for a partially deuterated compound is provided by G.A. Jeffrey *et al.*, *Neutron Diffraction Refinement of Partially Deuterated β-D-Arabinopyranose and α-L-Xylopyranose at 123 K*, B36 Acta Crystallographica 373-77 (1980) (incorporated by reference herein in its entirety). Jeffrey *et al.* used single-crystal neutron diffraction to determine the percentage deuterium substitution for hydroxyl groups on two sugar compounds of interest. Employing the methods discussed by Jeffrey *et al.*, one may similarly ascertain the isotopic ratio for a particular H/D position on a deuterated pomalidomide compound.

5.4 INHIBITION OF TNFα

[00177] Human peripheral blood mononuclear cells (hPBMC) from normal donors are obtained by Ficoll Hypaque (Pharmacia, Piscataway, NJ, USA) density centrifugation. Cells are cultured in RPMI 1640 (Life Technologies, Grand Island, NY, USA) supplemented with 10% AB+human serum (Gemini Bio-products, Woodland,

CA, USA), 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin (Life Technologies).

[00178] PBMC (2 x 10^5 cells) are plated in 96-well flat-bottom Costar tissue culture plates (Corning, NY, USA) in triplicate. Cells are stimulated with LPS (from Salmonella abortus equi, Sigma cat.no. L-1887, St.Louis, MO, USA) at 1 ng/ml final in the absence or presence of compounds. Compounds provided herein are dissolved in DMSO (Sigma) and further dilutions are done in culture medium immediately before use. The final DMSO concentration in all assays can be about 0.25%. Compounds are added to cells 1 hour before LPS stimulation. Cells are then incubated for 18-20 hours at 37°C in 5 % CO_2, and supernatants are then collected, diluted with culture medium and assayed for TNFα levels by ELISA (Endogen, Boston, MA, USA). IC_{50}s are calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100% and bottom to 0%, allowing variable slope (GraphPad Prism v3.02).

5.5 PRODUCTION OF IL-2

[00179] PBMC are depleted of adherent monocytes by placing 1 x 10^8 PBMC in 10 ml complete medium (RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin) per 10 cm tissue culture dish, in 37°C, 5 % CO_2 incubator for 30-60 minutes. The dish is rinsed with medium to remove all non-adherent PBMC. T cells are purified by negative selection using the following antibody (Pharmingen) and Dynabead (Dynal) mixture for every 1 x 108 non-adherent PBMC: 0.3 ml Sheep anti-mouse IgG beads, 15 μl anti-CD16, 15 μl anti-CD33, 15 μl anti-CD56, 0.23 ml anti-CD19 beads, 0.23 ml anti-HLA class II beads, and 56 μl anti-CD14 beads. The cells and bead/antibody mixture is rotated end-over-end for 30-60 minutes at 4°C. Purified T cells are removed from beads using a Dynal magnet. Typical yield is about 50% T cells, 87-95% $CD3^+$ by flow cytometry.

[00180] Tissue culture 96-well flat-bottom plates are coated with anti-CD3 antibody OKT3 at 5 μg/ml in PBS, 100 μl per well, incubated at 37°C for 3-6 hours, then washed four times with complete medium 100 μl/well just before T cells are added. Compounds are diluted to 20 times of final in a round bottom tissue culture 96-well plate. Final concentrations are about 10 μM to about 0.00064 μM. A 10 mM stock of compounds provided herein is diluted 1:50 in complete for the first 20x dilution of 200 μM in 2 % DMSO and serially diluted 1:5 into 2 % DMSO. Compound is added at 10

μl per 200 μl culture, to give a final DMSO concentration of 0.1 %. Cultures are incubated at 37°C, 5 % CO_2 for 2-3 days, and supernatants analyzed for IL-2 by ELISA (R&D Systems). IL-2 levels are normalized to the amount produced in the presence of an amount of a compound provided herein, and EC_{50}s calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope (GraphPad Prism v3.02).

5.6 POTENCIES

[00181] Potencies of racemic, (R)-, and (S)-pomalidomide in inhibiting TNFα were measured using procedures substantially similar to those described in Section 5.4 above. IC_{50}s for TNFα were determined to be 0.013 μM, 0.0933 μM and 0.0039 μM for racemic, (R)- and (S)-pomalidomide, respectively.

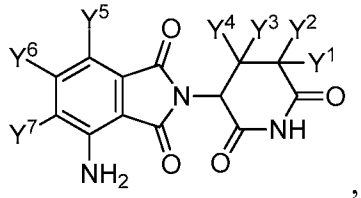
[00182] In addition, potencies of racemic, (R)-, and (S)-pomalidomide in promoting the production of IL-2 were measured using procedures substantially similar to those described in Section 5.5 above. EC_{50}s for IL-2 were determined to be 0.0103 μM, 0.0572 μM and 0.0124 μM for racemic, (R)- and (S)-pomalidomide, respectively.

[00183] All of the cited references are incorporated herein by reference in their entirety.

CLAIMS

What is claimed is:

1. A compound of the formula:



,

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:
at least one of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 is a hydrogen that is isotopically enriched with deuterium, and the others of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 are non-enriched hydrogen atoms.

2. The compound of claim 1, wherein one of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 is isotopically enriched with deuterium, and the others are non-enriched hydrogens.

3. The compound of claim 1, wherein two of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

4. The compound of claim 1, wherein three of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

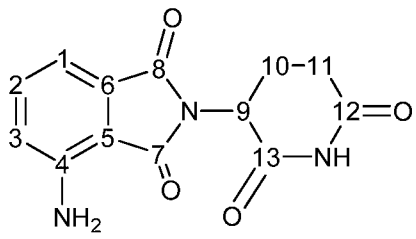
5. The compound of claim 1, wherein four of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

6. The compound of claim 1, wherein five of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

7. The compound of claim 1, wherein six of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

8. The compound of claim 1, wherein all of Y^1, Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 are isotopically enriched with deuterium.

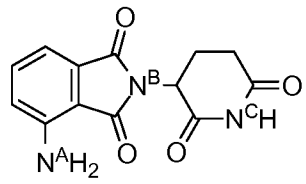
9. A compound of the formula:



,

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 are carbon atoms; and
at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 is isotopically enriched with carbon-13.

10. A compound of the formula:



,

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:
N^A, N^B, and N^C are nitrogen atoms; and
at least one of N^A, N^B, or N^C are isotopically enriched with nitrogen-15.

11. A pharmaceutical composition comprising a compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

12. A method of treating, managing or preventing a disease or disorder comprising administering to a patient a compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein the disease or disorder is cancer, a disorder associated with angiogenesis, pain, macular degeneration or a related syndrome, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis or a related disorder, dysfunctional sleep or a related disorder, hemoglobinopathy or a related disorder, or a TNFα related disorder.

13. The method of claim 12, further comprising administering a second active agent.

14. The compound of claim 1, 9 or 10, which is an (S)-isomer.

15. The compound of claim 1, 9 or 10, which is an (R)-isomer.