Title: ISOTOPOLOGUES OF THALIDOMIDE

Abstract: Provided herein are thalidomide, 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 THALIDOMIDE

1. FIELD
[0001] Provided herein are isotopologues of thalidomide, 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
[0002] 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 proneoplastic 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, L, Brostoff, J and Kale, D., Immunology, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

[0003] 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.

[0004] 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).

[0005] 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.

[0006] 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.

[0007] 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.

[0008] 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).
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.

Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, heparin 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).

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.

Thalidomide has the following chemical structure:

Thalidomide is described variously as: 2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione; α-(N-phthalimido) glutarimide; among other chemical names. Thalidomide and compositions comprising thalidomide 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**

[0013] Embodiments provided herein encompass particular isotopologues of thalidomide. Certain embodiments encompass mixtures of isotopologues. Certain embodiments encompass methods of synthesizing, isolating, or characterizing the isotopologues. In certain embodiments, the isotopologues of thalidomide are deuterium, carbon-13, or nitrogen-15 enriched.

[0014] In certain embodiments, provided herein are pharmaceutical compositions and single unit dosage forms comprising one or more isotopologues of thalidomide. 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 thalidomide.

4. **DETAILED DESCRIPTION**

4.1 **DEFINITIONS**

[0015] The descriptions of the terminology provided below apply to the terms as used herein and unless otherwise specified.

[0016] The term "compound" includes salts and solvates (e.g., hydrates) thereof.

[0017] 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.

[0018] 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 isotopically enriched composition other than the natural isotopic composition of that atom. As used herein, an "isotopologue" is an isotopically enriched compound.

[0019] 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%.

[0020] The term "isotopic enrichment factor" refers to the ratio between the isotopic composition and the natural isotopic composition of a specified isotope.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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."
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.

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.

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**

Provided herein are isotopically enriched compounds, including isotopically enriched thalidomide, synthetic intermediates thereof, and metabolites thereof.


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.

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)).

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.

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 T₂O. 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, ¹³C or ¹⁴C for carbon, ³³S, ³⁴S, or ³⁶S for sulfur, ¹⁵N for nitrogen, and ¹⁷O or ¹⁸O for oxygen, may lead to a similar kinetic isotope effect.

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.

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.

In some embodiments, provided herein are deuterated analogues of thalidomide, in which one or more atomic positions of the thalidomide molecule is/are isotopically enriched with deuterium. Certain embodiments herein provide compounds of the following chemical structure:

![Chemical Structure](image)

in which one or more Y atoms (i.e., Y1, Y2, Y3, Y4, Y5, Y6, Y7, or Y8) 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, seven, or eight of the indicated Y atoms is/are isotopically enriched with deuterium, and any remaining Y atom(s) is/are non-enriched hydrogen(s).

In certain embodiments, one or more Y atoms on the glutarimide portion of compound 1 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:
In certain embodiments, one or more Y atoms on the isoindoline portion of compound 1 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:
In certain embodiments, one or more Y atoms on both the glutarimide portion and the isoindoline portion of compound 1 are deuterium-enriched, i.e., any combination of deuteration shown above for the glutarimide portion and the isoindoline portion is encompassed.
It is understood that one or more deuteriums may exchange with hydrogen under physiological conditions.

In some embodiments, provided herein are carbon-13 analogues of thalidomide, in which on or more atomic positions of the thalidomide molecule is isotopically enriched with carbon-13. In certain embodiments, provided herein are compounds of the following chemical structure:

![Chemical Structure](image)

in which one or more of positions 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.

In certain embodiments, one or more carbon atom(s) of the glutarimide portion of compound 21, 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.
In certain embodiments, one or more carbon atom(s) on the isoindoline portion of compound 21, i.e., 1, 2, 3, 4, 5, 6, 7, or 8, is/are carbon-13-enriched. For example, particular compounds of compound 21 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.

In some embodiments, compounds of formula 21 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.

In some embodiments, compounds of formula 21 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, 5, 6, and 7; 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, 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.

[0046] In some embodiments, compounds of formula 21 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; 2, 3, 5, and 8; 3, 4, 6, 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, and 7; 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, 4, 6, 7, and 8; 2, 4, 6, 7, and 8; 2, 4, 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.

[0047] In some embodiments, compounds of formula 21 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, 4, 5, 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, 5, 7, and 8; 1, 3, 5, 6, 7, and 8; 1, 4, 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, 5, 7, and 8; 2, 3, 4, 6, 7, and 8; 2, 4, 5, 6, 7, and 8; 2, 4, 5, 6, 7, and 8; or 3, 4, 5, 6, 7, and 8.

[0048] In some embodiments, compounds of formula 21 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.

[0049] In certain embodiments, one or more carbon atoms on both the glutarimide portion and the isoindoline portion of compound 21 is/are carbon-13-enriched, i.e., any combination of isotopically-enriched positions shown above for the glutarimide portion and the isoisoindoline portion is encompassed.

[0050] In some embodiments, provided herein are nitrogen-15 analogues of thalidomide, in which one or more atomic positions of the thalidomide is isotopically enriched with
In certain embodiments, provided herein are compounds of the following chemical structure:

\[
\text{N^A}_1\text{N^B}_2
\]

in which N\text{A} or N\text{B} is/are isotopically enriched with nitrogen-15, and any remaining nitrogen atom(s) is/are non-enriched nitrogen atom(s).

[0051] In some embodiments, the compound has one of the following structures, wherein the asterisk * indicates a nitrogen-15 enriched atomic position, *i.e.*, a sample comprising the given compound has a nitrogen-15 enrichment at the indicated position(s) above the nature abundance of nitrogen-15.

\[54\]
\[55\]
\[56\]

[0052] 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

[0053] The compounds described herein may be synthesized using methods known to those of ordinary skill in the art. For example, particular compounds described herein are synthesized using standard synthetic organic chemistry techniques known to those of ordinary skill in the art.
In some embodiments, known procedures for the synthesis of thalidomide are employed, wherein one or more of the reagents, starting materials, precursors, or intermediates are replaced by one or more isotopically-enriched reagents or intermediates, including but not limited to one or more deuterium-enriched reagents, starting materials, precursors, or intermediates, one or more carbon-13-enriched reagents, starting materials, precursors, or intermediates, and/or one or more nitrogen-15-enriched reagents, starting materials, precursors, or intermediates. Such known procedures for the synthesis of thalidomide include, but are not limited to, those described in Reepmeyer et al., FDA monograph: Guidelines to Thalidomide Synthesis, U.S. Food & Drug Administration: Washington D.C., June 1987; Muller, U.S. Patent No. 5,463,063, and Muller et al., Organic Process Research & Development, 1999, 3, 139-140, both of which are incorporated herein by reference in their entireties. Isotopically enriched reagents, starting materials, precursors, and intermediates are commercially available or may be prepared by routine chemical reactions known to one of skill in the art.

Reepmeyer et al. described a procedure for synthesizing thalidomide starting from phthalic anhydride as shown in the scheme below.

![Scheme 1](image)

Muller described a procedure for synthesizing thalidomide starting from glutamine as shown in the scheme below. See, e.g., Muller, U.S. Patent No. 5,463,063, incorporated herein by reference in its entirety.
In some embodiments, one or more hydrogen positions of the glutarimide portion of thalidomide are enriched with deuterium through organic synthesis. In some embodiments, the methods of Reepmeyer et al. are employed. In particular embodiments, the methods of Reepmeyer et al. are employed, wherein a deuterium-enriched glutamic acid (formula 57) is used in the reaction with phthalic anhydride, as shown in the scheme below:

wherein one or more $Y$ atoms (i.e., $Y^5$, $Y^6$, $Y^7$, or $Y^8$) 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, or four of the indicated $Y$ atoms is/are isotopically enriched with deuterium, and any remaining $Y$ atom(s) is/are non-enriched hydrogen(s). Compounds of formula 57 may be obtained commercially or through techniques known to those of skill in the art.

In some embodiments, the methods described in U.S. Patent No. 5,463,063 are employed. In particular embodiments, the methods of U.S. Patent No. 5,463,063 are
employed, wherein a deuterium enriched glutamine is used, as shown in the following scheme:

![Scheme 4](image)

wherein one or more Y atoms (i.e., Y^5, Y^6, Y^7, or Y^8) 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, or four of the indicated Y atoms is/are isotopically enriched with deuterium, and any remaining Y atom(s) is/are non-enriched hydrogen(s).

Compounds of formula 57a may be obtained commercially or through techniques known to those of skill in the art.

[0059] In some embodiments, one or more hydrogen positions of the isoindoline portion are enriched with deuterium through organic synthesis. In certain embodiments, thalidomide is subjected to reaction conditions suitable for the deuteration of the aromatic ring as shown in the following scheme.

![Scheme 5](image)

In some embodiments, one or more hydrogen positions of the isoindoline portion are enriched with deuterium following the methods of Reepmeyer et al. or U.S. Patent No. 5,463,063, wherein a deuterium-enriched phthalic anhydride (formula 59) is used in the reaction with glutamic acid or glutamine, as shown in the scheme below:

Scheme 6

wherein one or more Y atoms (i.e., Y^1, Y^2, Y^3, or Y^4) 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, or four of the indicated Y atoms is/are isotopically enriched with deuterium, and any remaining Y atom(s) is/are non-enriched hydrogen(s). Compounds of formula 59 may be obtained commercially or through techniques known to those of skill in the art.

In some embodiments, one or more hydrogen positions of the glutarimide portion and one or more hydrogen positions of the isoindoline portion are enriched with deuterium through organic synthesis. In particular embodiments, the methods of Reepmeyer et al. or U.S. Patent No. 5,463,063 are employed, wherein a deuterium-enriched glutamic acid (formula 57) or deuterium-enriched glutamine (formula 57a) is reacted with deuterium-enriched phthalic anhydride (formula 59), as shown in the scheme below:
wherein one or more Y atoms (i.e., Y₁, Y₂, Y₃, Y₄, Y₅, Y₆, or Y₇) 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).

[0063] In certain embodiments, one or more carbon positions of the glutarimide portion are enriched with ¹³C through organic synthesis. In particular embodiments, the methods of Reepmeyer et al. or U.S. Patent No. 5,463,063 are employed, wherein a carbon-13 enriched glutamic acid (formula 60) of carbon-13 enriched glutamine (formula 60a) is used in the reaction with phthalic anhydride, as shown in the scheme below:

Scheme 8
wherein one or more of 9, 10, 11, 12, and 13 is/are carbon atom(s) that is/are 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, or five of 9, 10, 11, 12, and 13 is/are isotopically enriched with carbon-13, and any remaining carbon atom(s) is/are non-enriched carbon atom(s). Compounds of formula 60 may be obtained commercially or through techniques known to those of skill in the art.

[0064] In some embodiments, one or more carbon positions of the isoindoline portion are enriched with carbon-13 following the methods of Reepmeyer et al. or U.S. Patent No. 5,463,063, wherein a carbon-13-enriched phthalic anhydride (formula 61) is used in the reaction with glutamic acid or glutamine, as shown in the scheme below:

![Scheme 9](image)

Scheme 9

wherein one or more of 1, 2, 3, 4, 5, 6, 7, or 8 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, or eight of 1, 2, 3, 4, 5, 6, 7, or 8 is/are isotopically enriched with carbon-13, and any remaining carbon atom(s) is/are non-enriched carbon atom(s). Compounds of formula 61 may be obtained commercially or through techniques known to those of skill in the art.

[0065] In some embodiments, one or more carbon positions of the glutarimide portion and one or more carbon positions of the isoindoline portion are enriched with deuterium through organic synthesis. In particular embodiments, the methods of Reepmeyer et al. or U.S. Patent No. 5,463,063 are employed, wherein a carbon-13-enriched glutamic acid or (formula 60) or carbon-13-enriched glutamine (formula 60a) is reacted with carbon-13-enriched phthalic anhydride (formula 61), as shown in the scheme below:
wherein one or more of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 is/are carbon atoms 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 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 carbon atom(s).

[0066] In some embodiments, the nitrogen of the glutarimide portion is enriched with nitrogen-15 though organic synthesis. In particular embodiments, the methods of Reepmeyer et al. are employed, wherein a nitrogen-15-enriched urea (formula 62) is used, as shown in the scheme below. Compound 62 is available from commercial sources.

Scheme 10

[0067] In another embodiment, the methods of U.S. Patent No. 5,463,063 are employed, wherein a nitrogen-15 enriched glutamine is used, as used in the scheme below.
In some embodiments, the nitrogen of the isoindoline portion is enriched with nitrogen-15 through organic synthesis. In particular embodiments, the methods of Reepmeyer et al. or U.S. Patent No. 5,463,063 are employed, wherein a nitrogen-15-enriched glutamic acid (formula 63) or glutamine (formula 63a) is reacted with phthalic anhydride, as shown in the scheme below. Compound 63 is available from commercial sources.

In some embodiments, both nitrogen atoms of thalidomide are enriched with nitrogen-15 through organic synthesis. In particular embodiments, the methods of Reepmeyer et al. are employed, wherein a nitrogen-15-enriched urea (formula 62) and nitrogen-15-enriched glutamic acid (formula 63) are used, as shown in the scheme below.
In some embodiments, the methods of U.S. Patent No. 5,463,063 are employed, wherein nitrogen-15-enriched glutamine is used, as shown in the scheme below.

The routes and methods described above can be modified to provide an isotopologues of thalidomide having both deuterium enrichment and carbon-13 enrichment; both deuterium enrichment and nitrogen-15 enrichment; both carbon-13 enrichment and nitrogen-15 enrichment; or deuterium enrichment, carbon-13 enrichment, and nitrogen-15 enrichment.

4.3 METHODS OF TREATMENT, PREVENTION AND MANAGEMENT

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.

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.

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.

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.

[0076] 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 myeloblasts 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, fibrodyplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable 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.

[0077] 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 myeloblasts 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.

[0078] 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 myeloblasts 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.

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 to 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 mantle zone lymphoma).

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.

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.

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.
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.

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).

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).

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.

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.

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-Trelat, 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).

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 arterialopathy (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 vascular 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.

[0090] 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.

[0091] 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.

[0092] 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-telangiectasia, 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.

[0093] 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
references. 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.

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.

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 erythematosus, ENL in leprosy, radiation damage, cancer, asthma, or hyperoxic alveolar injury.

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:

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

[0097] 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.

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.

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 entirety 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, sepsis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, 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.

[00100] 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.

[00101] 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

[00102] 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*.

[00103] 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).

[00104] 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 deacetylase 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 acyltransferase 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 (Ovnitarg™)); 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).

[00105] Specific second active compounds that can be combined with compounds provided herein vary depending on the specific indication to be treated, prevented or managed.

[00106] For instance, for the treatment, prevention or management of cancer, second active agents include, but are not limited to: semaxanib; cyclosporin; etanercept; doxycycline; bortezomib; aciclovir; aclacinomycin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; amelantrone 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; carubcin hydrochloride; carzelesin; cedefmgol; cedecoxib; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbose; dactinomycin; daunorubicin
Other second agents include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclacinomycin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambustine; amidox; amidostine; amnilevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; fludarabine phosphate; fluorouracil; flurocitabine; 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; masoprol; maytansine; mechloretamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitoxantrone hydrochloride; mitomalcin; mitomycin; mitomycin C; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peplomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safmgol; safmgol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptogargin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; tereoxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulazole hydrochloride; uracil mustard; uredepa; vaproetide; 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.
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; benzchlorins; benzoylstaurosporine;
beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor;
bicalutamide; bisantrene; bisaziridinylspermine; bisafide; bistratene A; bizelesin; breflate;
bropirimine; budotitane; buthionine sulfoximine; calcapotriol; 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; cytoytic factor; cytostatin; dacliximab;
decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dextifosfamide; dexrazoxane;
dexverapamil; diaziquone; didemnin B; didox; diethylorspermine; dihydro-5-azacytidine;
dihydropyrazol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron;
doxifuridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine;
edelfosine; edrecolomab; eflorenthine; elemene; emitefur; eprubicin; epristeride;
estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide
phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride;
flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride;
forfenimex; foremestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate;
galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam;
heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene;
idramantone; ilmofo sine; ilomatstat; imatinib (Gleevec®), imiquimod; immunostimulant
peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons;
interleukins; iboguanine; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine;
isobengazole; isohomohalicondrin B; itasetron; ja splakinolide; kahalalide F; lamellarin-N
triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; letolstatin; letrozole;
leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone;
leupreol in; levamisole; liarozone; linear polynamine 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; mitotakin 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; 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; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentoan polysulfate sodium; pentostatin; pentrozole; perfluorbenzyl 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 Bl; ruboxyl; safmgol; 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; sulfmosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfm; 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; vindes; verteporfm; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stilamaler.

[00108] Specific second active agents include, but are not limited to, 2-methoxyestradiol, telomestatin, inducers of apoptosis in multiple 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-I 1, interferon alpha, pegylated interferon alpha (e.g., PEG INTRON-A), capecitabine, cisplatin, thiopeta, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitonate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil ®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt ®), sulindac, and etoposide.

[00109] 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.

[00110] 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 analogs, 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®), bretylum, ketanserin, reserpine, droperidol, atropine, phenotolamine, 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.

[00111] 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 sensitizier, 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-l,21-dihydroxy-16, 17-l-methylethylidinebis(oxy)pregna-l,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'-0-MaI genistin, 6'-0-Ac genistin, daidzein, daidzin, 6'-0-MaI daidzin, 6'-0-Ac daidzin, glycitein, glycitin, 6'-0-MaI glycitin, biochanin A, formononetin (U.S. Patent No. 6,001,368), triamcinolone acetonide, 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), EYEIOI (Eyetech Pharmaceuticals), LY333531 (Eli Lilly), Miravant, and RETISERT implant (Bausch & Lomb). All of the references cited herein are incorporated in their entirety by reference.

[00112] 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.

Examples of second active agents that may be used for the treatment, prevention and/or management of pulmonary hypertension 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 12 (PGI2), epoprostenol (EPO, Floran®), treprostinil (Remodulin®), nitric oxide (NO), bosentan (Tracleer®), amldipine, epoprostenol (Floran®), treprostinil (Remodulin®), prostacyclin, tadalafil (Cialis®), simvastatin (Zocor®), omapatrilat (Vanlev®), irbesartan (Avapro®), pravastatin (Pravachol®), digoxin, L-arginine, iloprost, betaprost, and sildenafil (Viagra®).

Examples of second active agents that may be used for the treatment, prevention and/or management of asbestos-related diseases 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, thiopeta, fludarabine, carboplatin, liposomal daunorubicin, cytarbaine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphophonate, arsenic trioxide, vincristine, doxorubicin (Dox®), paclitaxel, ganciclovir, adriamycin, bleomycin, hyaluronidase, mitomycin C, mepacrine, thiopeta, tetracycline and gemcitabine.

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 stibogluconurate), interferene gamma, itraconazole, a combination of dead promastigotes and BCG, leucovorin, corticosteroids, sulfonamide, spiramycin, IgG (serology), trimethoprim, and sulfamethoxazole.
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, levamisole and isopropinosine; biologies 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).

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, L-DOPA, cocaine, α-methyltyrosine, reserpine, tetrabenazine, benzotropine, pargyline, fenoldopam mesylate, cabergoline, pramipexole dihydrochloride, ropinorele, 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 salicylate, physostigmine sulfate, physostigmine bromide, meostigmine bromide, neostigmine methylsulfate, ambenonim chloride, edrophonium chloride, tacrine, pralidoxime chloride, obidoxime chloride, trimeproxide 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, tolfenin, ketorolac, dichlofenac, flurbinoprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, dromanxim, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, naproxen, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone and benzbromarone or betamethasone and other glucocorticoids;
and an antiemetic agent, such as, but not limited to, metoclopramide, 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, oxypernydyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thaliophenazine, thioproperazine, tropisetron, and a mixture thereof.

[00118] 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, acetyaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbiprofen, 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 1-threo-methylphenidate, d-threo-methylphenidate, dl-threo-methylphenidate, 1-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.

[00119] 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
antiarythmic 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, oxycodone, morphine, topiramate, amitriptyline, nortriptyline, carbamazepine, Levodopa, L-DOPA, cocaine, α-methyl-tyrosine, reserpine, tetrabenazine, benzotropine, pargyline, fenodolpam mesylate, cabergoline, pramipexole dihydrochloride, ropinirole, amantadine hydrochloride, selegiline hydrochloride, carbidopa, pergolide mesylate, Sinemet CR, Symmetrel, iproniazid, clorgyline, phenelzine, isocarboxazid, tolcapone, entacapone, physostigmine salicylate, physostigmine sulfate, physostigmine bromide, meostigmine bromide, neostigmine methylsulfate, ambenonium 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, diclofenac, flurbiprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, d Roxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfipyrazone, 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, scopalamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and a mixture thereof.

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-nl, interferon alfa-n3, interferon beta-1 a, and interferon gamma-I b; and G-CSF; hydroxyurea; butyrates or butyrate derivatives; nitrous oxide; hydroxyurea; 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).

[00121] 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 (60th ed., 2006).

[00122] 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.

[00123] 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

[00124] 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.
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.

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.

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.

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

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.

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.
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.

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).

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.

[00134] 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, pregelatinized starch, and magnesium stearate.

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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

[00141] 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).

[00142] 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.

[00143] 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.

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.

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.

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.

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.

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.

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.

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 laurate, 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 Piano, 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.

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

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.

[00153] 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.

[00154] 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

[00155] 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.
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.

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

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.

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).

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**

[00161] 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.

[00162] 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).

[00163] 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.

[00164] 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**

[00165] Isotopically enriched analogs of the compounds provided herein may generally be prepared according known procedures for the synthesis of thalidomide, 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 **EXAMPLE 1**

[00166] The isoindoline portion of thalidomide is deuterated by subjecting thalidomide to conditions suitable for aromatic deuteration, which are known 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. For example, thalidomide is treated with D\textsubscript{2}O over 5% Pt/C under hydrogen gas to provide a compound of formula 58, as depicted in the following scheme.

![Scheme 16](image)

5.2 **EXAMPLE 2**

[00167] The glutarimide portion of thalidomide is enriched with deuterium through the methods of Reepmeyer et al., as shown in the scheme below.
Phthalic anhydride (compound 64) and deuterium-enriched glutamic acid (compound 65), which is commercially available, is refluxed in pyridine for about 4 hours and subsequently concentrated to obtain N-phthalylglutamic acid (compound 66). Compound 66 is then mixed in acetic anhydride overnight to obtain N-phthalylglutamic anhydride (compound 67), which is isolated by filtration and washed with dry ethyl ether. Compound 67 is mixed with urea at 205-212°C under nitrogen for about 1 hour to obtain deuterium-enriched thalidomide (compound 9), which is purified by recrystallization.

**5.3 EXAMPLE 3**

Compound 3 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available compound 68, as shown in the scheme below.

**5.4 EXAMPLE 4**

Compound 20 is obtained under the same conditions as example 2 by replacing compound 64 with commercially available compound 69, as shown in the scheme below.
5.5 **EXAMPLE 5**

[00171] Compound 70 is obtained under the same conditions as example 2 by replacing compound 64 with commercially available compound 69, as shown in the scheme below.

![Scheme 19]

5.6 **EXAMPLE 6**

[00172] Compound 71 is obtained under the same conditions as example 2 by replacing compound 64 with commercially available compound 69 and replacing compound 65 with commercially available compound 68, as shown in the scheme below.

![Scheme 20]

5.7 **EXAMPLE 7**

[00173] Compound 36 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available compound 72, as shown in the scheme below.
5.8 **EXAMPLE 8**

[00174] Compound 22 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available compound 73, as shown in the scheme below.

\[
\begin{align*}
\text{HOOC-
\begin{array}{c}
\text{C}-
\end{array}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{HOOC-
\begin{array}{c}
\text{C}-
\end{array}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

* = carbon-13-enriched carbon atom

**Scheme 22**

5.9 **EXAMPLE 9**

[00175] Compound 27 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available compound 74, as shown in the scheme below.

\[
\begin{align*}
\text{HOOC-
\begin{array}{c}
\text{C}-
\end{array}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{HOOC-
\begin{array}{c}
\text{C}-
\end{array}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

* = carbon-13-enriched carbon atom

**Scheme 23**

5.10 **EXAMPLE 10**

[00176] Compound 31 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available compound 75, as shown in the scheme below.
5.11 EXAMPLE 11

[00177] Compound 34 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available compound 76, as shown in the scheme below.

75

\[
\begin{array}{c}
\text{HO}^*\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{O}^* \\
\text{NH}_2
\end{array}
\rightarrow
\begin{array}{c}
\text{O}^*\text{N}^\equiv\text{C}^\equiv\text{C}^\equiv\text{N}^* \\
\text{O}^*\text{N}^\equiv\text{C}^\equiv\text{C}^\equiv\text{N}^* \\
\text{O}^*\text{N}^\equiv\text{C}^\equiv\text{C}^\equiv\text{N}^*
\end{array}
\]

31

* = carbon-13-enriched carbon atom

Scheme 25

5.12 EXAMPLE 12

[00178] Compound 77 is obtained under the same conditions as example 2 by replacing compound 64 with commercially available compound 78, as shown in the scheme below.

76

\[
\begin{array}{c}
\text{HO}^*\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{O}^* \\
\text{NH}_2
\end{array}
\rightarrow
\begin{array}{c}
\text{O}^*\text{N}^\equiv\text{C}^\equiv\text{C}^\equiv\text{N}^* \\
\text{O}^*\text{N}^\equiv\text{C}^\equiv\text{C}^\equiv\text{N}^* \\
\text{O}^*\text{N}^\equiv\text{C}^\equiv\text{C}^\equiv\text{N}^*
\end{array}
\]

34

* = carbon-13-enriched carbon atom

Scheme 26

5.13 EXAMPLE 13

[00179] Compound 81 is obtained under the same conditions as example 2 by replacing compound 64 with compound 80, which is synthesized by the reaction of commercially available carbon-13-enriched phthalic acid (compound 79) with acetic anhydride or oxalyl chloride or other conditions known in the art, such as those described in Larock, R., *Comprehensive Organic Transformations*, 2nd ed., Wiley page 1930 (1999), which is incorporated herein by reference in its entirety, as shown below.
Carbon-13 enrichment of both the glutarimide moiety and isoindoline moiety is accomplished under the same conditions as example 2 by replacing compound 64 with commercially available compound 78 and replacing compound 65 with the appropriate carbon-13-enriched glutamic acid. For example, when compound 64 is replaced with compound 78 and compound 65 is replaced with compound 72, compound 82 is obtained, as shown in the scheme below.

* = carbon-13-enriched carbon atom

**Scheme 28**

**EXAMPLE 14**

[00180] Compound 54 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available nitrogen-15-enriched glutamic acid (compound 63), as shown below.

* = carbon-13-enriched carbon atom

**Scheme 29**

**EXAMPLE 15**

[00181]
5.16 **EXAMPLE 16**

Compound 55 is obtained under the same conditions as example 2 by replacing compound 68 with commercially available nitrogen-15-enriched urea (compound 62), as shown in the scheme below.

![Scheme 31](image)

5.17 **EXAMPLE 17**

Compound 56 is obtained under the same conditions as example 2 by replacing compound 65 with commercially available nitrogen-15-enriched glutamic acid (compound 83) and by replacing compound 68 with commercially available nitrogen-15-enriched urea (compound 62), as shown in the scheme below.

![Scheme 32](image)
Deuterium-enrichment, carbon-13-enrichment, and nitrogen-15-enrichment of thalidomide is accomplished under the same conditions as example 2 by use of the appropriate isotopically enriched reagents, starting materials, intermediates, or precursors. For example, compound 83 is obtained by replacing compound 64 with commercially available compound 78 and replacing compound 68 with commercially available compound 62, as shown in the scheme below.

* = carbon-13-enriched carbon atom

Scheme 33

In a further example, as shown in the scheme below, compound 85 is obtained by replacing compound 64 with compound 80 and replacing compound 68 with commercially available compound 62 to form compound 84, which is subjected to aromatic deuteration conditions, which are known 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.
The glutarimide portion of thalidomide is enriched with deuterium through the methods of U.S. Patent No. 5,463,063, as shown in the scheme below.
A mixture of deuterium enriched glutamine and sodium carbonate in water is rapidly added N-carbethoxyphthalimide as a solid. After 1 hour, the reaction mixture is filtered to remove unreacted N-carbethoxyphthalimide. The pH of the stirred filtrate is adjusted to 3-4 with 4N HCl. The mixture is then seeded with N-phthaloyl-L-glutamine and the pH adjusted to 1-2 with 4N HCl. The resulting slurry is stirred for 1 hour. The slurry is filtered and the solid washed with water. The solid is dried to afford N-phthaloyl-L-glutamine. N-phthaloyl glutamine, carbonyldiimidazole, and 4-dimethylaminopyridine in anhydrous THF is heated to reflux for 16 hours. The reaction slurry is filtered and the solid washed with methylene chloride. The solid is dried to provide deuterium-enriched thalidomide. Carbon-13 enrichment and nitrogen-15 enrichment of thalidomide may be achieved using similar methods by utilizing the appropriate carbon-13 or nitrogen-15 labeled glutamine starting material.

5.20 DETERMINATION OF ISOTOPIC ENRICHMENT

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.

Isotopic enrichment may also be confirmed by single-crystal neutron diffraction. For example, the isotopic ratio at a particular hydrogen/deuterium position in a deuterated thalidomide 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.

[00190] A single crystal of suitable size and quality comprising the deuterated thalidomide
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 thalidomide
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 thalidomide compound in a solvent with
appreciable solubility, then slowly diffusing into the solution of antisolvent (i.e., a solvent in
which the deuterated thalidomide 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).

[00191] After isolating a suitable single crystal comprising the deuterated thalidomide
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).

[00192] 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.

[00193] 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).

[00194] 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 & LyIe 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).

[00195] The isotopic ratio for a particular position on a deuterated thalidomide 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 ah, Neutron Diffraction Refinement of Partially Deuterated \( B\)-D-Arabinopyranose and \( a\)-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 thalidomide compound.

[00196] All of the cited references are incorporated herein by reference in their entirety.
What is claimed is:

1. A compound of the formula:

   ![Chemical Structure]

   or a pharmaceutically acceptable salt or solvate thereof, wherein:
   at least one of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ is a hydrogen that is isotopically enriched with deuterium, and the others of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ are non-enriched hydrogen atoms.

2. The compound of claim 1, wherein one of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ is isotopically enriched with deuterium, and the others are non-enriched hydrogens.

3. The compound of claim 1, wherein two of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

4. The compound of claim 1, wherein three of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

5. The compound of claim 1, wherein four of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

6. The compound of claim 1, wherein five of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

7. The compound of claim 1, wherein six of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ are isotopically enriched with deuterium, and the others are non-enriched hydrogens.

8. The compound of claim 1, wherein seven of $Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^7,$ and $Y^8$ are isotopically enriched with deuterium, and the others are non-enriched hydrogens.
9. The compound of claim 1, wherein all of $Y_1$, $Y_2$, $Y_3$, $Y_4$, $Y_5$, $Y_6$, $Y_7$, and $Y_8$ are isotopically enriched with deuterium, and the other is non-enriched hydrogens.

10. A compound of the formula:

\[
\begin{array}{c}
\text{2} \quad \text{6} \quad \text{8} \\
\text{4} \quad \text{5} \quad \text{9} \\
\end{array}
\]

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.

11. A compound of the formula:

\[
\begin{array}{c}
\text{O} \\
\text{N}^\text{A} \quad \text{N}^\text{B} \\
\text{O} \\
\end{array}
\]

wherein $N^A$ and $N^B$ are nitrogen atoms;

and at least one of $N^A$ or $N^B$ is isotopically enriched with nitrogen-15.

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

13. 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 11, or a pharmaceutically acceptable salt or solvate 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 TNF$\alpha$ related disorder.
14. The method of claim 13, further comprising administering a second active agent.
A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 A61K31/454 A61P35/00

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABSTRACTS, EMBASE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
</table>
| X,P      | YAMAMOTO T ET AL: "Synthesis and configurational stability of (S)- and (R)-
| Y,P      | figure 1                                                                         | 3-11,13, 14 |

Further documents are listed in the continuation of Box C

D

See patent family annex

Date of the actual completion of the international search

19 July 2010

Name and mailing address of the ISA/Authorized officer

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040,
Fax (+31-70) 340-3016

Kol imannsberger, M

Date of mailing of the international search report
30/07/2010
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>RHODES, HAROLD J. ET AL: &quot;Synthesis of 2,6-dioxo-3-phthalimidopiperidine-3,4,4,5,5-d5 and 2,5-dioxo-3-phthalimidoppyrrole-3,4,4-d3 from L-deuterioglutamic acid and L-deuterioaspartic acid&quot; JOURNAL OF PHARMACEUTICAL SCIENCES, 54(10), 1440-3 CODEN: JPMSAE; ISSN: 0022-3549, 1965, XP002592522</td>
<td>1, 6, 12</td>
</tr>
<tr>
<td>Y</td>
<td>the whole document</td>
<td>2-5, 7-11, 13, 14</td>
</tr>
<tr>
<td>Y</td>
<td>page 1529, column 1, line 6 - line 8; figure 1</td>
<td>1-9, 11, 13, 14</td>
</tr>
</tbody>
</table>
| Y        | MELCHERT ET AL: "The thalidomide saga" INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, EXETER, GB LNKD-