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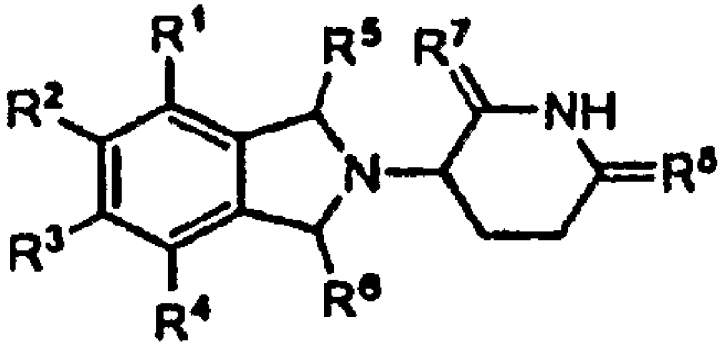
(54) **Title**: THIOXOISOINDOLINE COMPOUNDS AND COMPOSITIONS AND METHODS OF USING THE SAME

(I)



(57) **Abstract**: Provided are thioxo isoindoline compounds, and pharmaceutically acceptable salts, solvates, and stereoisomers, thereof. Methods of use, and pharmaceutical compositions of these compounds are disclosed. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of R^1-R^4 is NH_2 or NO_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; and R^7 and R^8 are each indepently thioxo or oxo.

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THIOXOISOINDOLINE COMPOUNDS AND COMPOSITIONS AND METHODS OF USING THE SAME

1. FIELD

[1] Provided herein are thioxo isoindoline compounds. Pharmaceutical compositions comprising the compounds and methods for treating, preventing and managing various disorders are also disclosed.

2. BACKGROUND

2.1 PATHOBIOLOGY OF CANCER AND OTHER DISEASES

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

[3] There is an enormous variety of cancers which are described in detail in the medical literature. Examples includes 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.

[4] 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).

[5] 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.

[6] 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.

2.2 METHODS OF TREATING CANCER

[7] 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.

[8] 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).

[9] 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.

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

[11] 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.

3. SUMMARY

[12] Provided herein are thioxo isoindoline compounds, and pharmaceutically acceptable salts, solvates (*e.g.*, hydrates), or stereoisomers thereof.

[13] Also provided are methods of treating and managing various diseases or disorders. The methods comprise administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[14] Also provided herein are methods of preventing various diseases and disorders, which comprise administering to a patient a prophylactically effective amount of a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[15] Also provided herein are pharmaceutical compositions, single unit dosage forms, dosing regimens and kits which comprise a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

4. DETAILED DESCRIPTION

[16] In one embodiment, provided are thioxo isoindoline compounds, and pharmaceutically acceptable salts, solvates, and stereoisomers thereof.

[17] In another embodiment, provided are methods of treating, managing, and preventing various diseases and disorders, which comprises administering to a patient a therapeutically or prophylactically effective amount of a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. Examples of diseases and disorders are described herein.

[18] In other embodiments, a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered in combination with another drug ("second active agent") or treatment. Second active agents include small molecules and large molecules (*e.g.*, proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of compounds provided herein include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage various disorders described herein.

[19] Also provided are pharmaceutical compositions (*e.g.*, single unit dosage forms) that can be used in the methods provided herein. In one embodiment, pharmaceutical compositions comprise a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and optionally a second active agent.

4.1 DEFINITION

[20] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All cited patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[21] As used herein, and unless otherwise specified, the term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids such as, but not limited to, acetic, alginic, anthranilic, benzenesulfonic,

benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, gluconic, glutamic, glucorenic, galacturonic, glycidic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, propionic, phosphoric, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, p-toluenesulfonic and the like.

[22] As used herein, and unless otherwise specified, the term "solvate" means a compound that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

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

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

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

[26] As used herein, and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center. Similarly, the term "enantiomerically enriched" means a stereomerically enriched composition of a compound having one chiral center.

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

[28] As used herein, and unless otherwise specified, 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. The terms "treat," "treating" and "treatment" refer to the administration of the compound provided herein, with or without other additional active agent, after the onset of symptoms of the particular disease.

[29] As used herein, and unless otherwise specified, 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. The terms "prevent," "preventing" and "prevention" refer to the treatment with or administration of the compound provided herein, with or without other additional active compound, prior to the onset of symptoms, to patients at risk of the disease described herein.

[30] As used herein, and unless otherwise specified, 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.

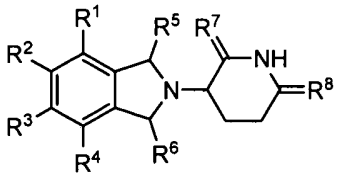
[31] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or disorder, or to delay or minimize one or more symptoms associated with the disease or disorder. 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.

[32] As used herein, and unless otherwise specified, 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

[33] In one embodiment, the compounds provided herein have formula (I):



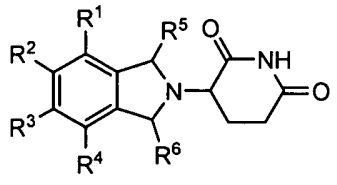
(I),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein one of R^1-R^4 is NH_2 or NO_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; and R^7 and R^8 are each independently thioxo or oxo.

[34] In one embodiment, the compounds provided herein have formula (I), wherein one of R^1-R^4 is NH_2 or NO_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; and R^7 and R^8 are each independently thioxo or oxo, provided that at least one of R^7 or R^8 is oxo.

[35] In one embodiment, the compounds provided herein have formula (I), wherein one of R^1-R^4 is NH_2 or NO_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; and R^7 and R^8 are each oxo. In one embodiment, the compounds provided herein have formula (I), wherein one of R^1-R^4 is NH_2 or NO_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; R^7 is thioxo and R^8 is oxo. In one embodiment, the compounds provided herein have formula (I), wherein one of R^1-R^4 is NH_2 or NO_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; R^8 is thioxo and R^7 is oxo. In one embodiment, the compounds provided herein have formula (I), wherein one of R^1-R^4 is NH_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; and R^7 and R^8 are each oxo.

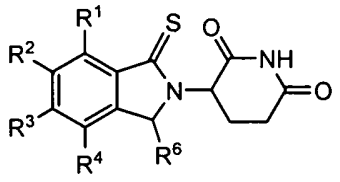
[36] In another embodiment, provided herein are compounds of formula (II):



(II),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein the variables are as described elsewhere herein.

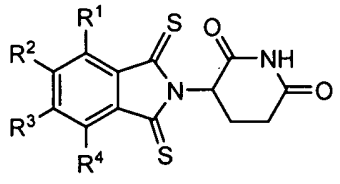
[37] In another embodiment, provided herein are compounds of formula (III):



(III),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein the variables are as described elsewhere herein.

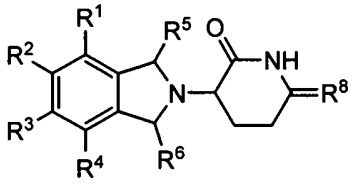
[38] In another embodiment, provided herein are compounds of formula (IV):



(IV),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein the variables are as described elsewhere herein.

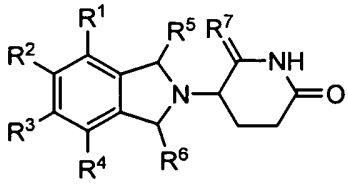
[39] In another embodiment, provided herein are compounds of formula (V):



(V),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein the variables are as described elsewhere herein.

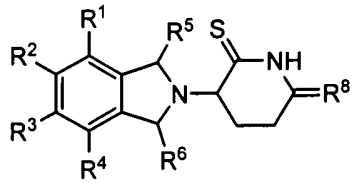
[40] In another embodiment, provided herein are compounds of formula (VI):



(VI),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein the variables are as described elsewhere herein.

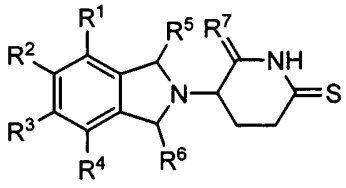
[41] In another embodiment, provided herein are compounds of formula (VII):



(VII),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein the variables are as described elsewhere herein.

[42] In another embodiment, provided herein are compounds of formula (VIII):



(VIII),

and pharmaceutically acceptable salts, solvates, and stereoisomers thereof, wherein the variables are as described elsewhere herein.

[43] In one embodiment, R^1 is NH_2 and R^2, R^3 and R^4 are each hydrogen. In one embodiment, R^2 is NH_2 and R^1, R^3 and R^4 are each hydrogen. In one embodiment, R^3 is NH_2 and R^1, R^3 and R^4 are each hydrogen. In one embodiment, R^4 is NH_2 and R^1, R^2 and R^3 are each hydrogen. In one embodiment, R^1 is NO_2 and R^2, R^3 and R^4 are each hydrogen. In one embodiment, R^2 is NO_2 and R^1, R^3 and R^4 are each hydrogen. In one embodiment, R^3 is NO_2 and R^1, R^3 and R^4 are each hydrogen. In one embodiment, R^4 is NO_2 and R^1, R^2 and R^3 are each hydrogen. In one embodiment, R^7 is oxo and R^8 is thioxo. In one embodiment, R^7 is thioxo and R^8 is oxo.

[44] In one embodiment, the compound is 3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[45] In one embodiment, the compound is 3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or 3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[46] In one embodiment, the compound is (R)-3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione, (R)-3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable salt or solvate thereof.

[47] In one embodiment, the compound is (S)-3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione, (S)-3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable salt or solvate thereof.

[48] In one embodiment, the compound is (R)-3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (R)-3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (R)-3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or (R)-3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione a pharmaceutically acceptable salt or solvate thereof.

[49] In one embodiment, the compound is (S)-3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (S)-3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (S)-3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or (S)-3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione a pharmaceutically acceptable salt or solvate thereof.

[50] In one embodiment, the compound is 3-(4-amino-1-thioxo-1,3-dihydroisoindol-2-yl)-6-thioxo-piperidin-2-one or 3-(4-nitro-1-thioxo-1,3-dihydroisoindol-2-yl)-6-thioxo-piperidin-2-one.

4.3 METHODS OF TREATMENT, PREVENTION AND MANAGEMENT

[51] 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), 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 cetain 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.

[52] 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.

[53] 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 patent no. 7,189,740 (Treatment of Myelodysplastic Syndrome); publication nos. 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.

[54] 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.

[55] Other specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, metastatic melanoma (localized melanoma, including, but not limited to, ocular melanoma), malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate

cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation.

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

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

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

[59] 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.

[60] 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.

[61] 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.

[62] 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.

[63] 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).

[64] 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

neovascularisation (CNVM), retinal pigment epithelium detachment (PED), and atrophy of retinal pigment epithelium (RPE).

[65] 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.

[66] 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.

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

[68] Examples of pulmonary disorders include, but are not limited to, those described in U.S. publication no. 2005/0239842A1, published October 27, 2005, which is incorporated herein by reference. Specific examples include pulmonary hypertension and related disorders. Examples of pulmonary hypertension and related disorders include, but

are not limited to: primary pulmonary hypertension (PPH); secondary pulmonary hypertension (SPH); familial PPH; sporadic PPH; precapillary pulmonary hypertension; pulmonary arterial hypertension (PAH); pulmonary artery hypertension; idiopathic pulmonary hypertension; thrombotic pulmonary arteriopathy (TPA); plexogenic pulmonary arteriopathy; functional classes I to IV pulmonary hypertension; and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vasular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus including systemic and cutaneous lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

[69] 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.

[70] 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.

[71] Examples of immunodeficiency disorders include, but are not limited to, those described in U.S. application no. 11/289,723, filed November 30, 2005. Specific examples include, but not limited to, adenosine deaminase deficiency, antibody deficiency with normal or elevated Igs, ataxia-tenlangiectasia, bare lymphocyte syndrome, common variable immunodeficiency, Ig deficiency with hyper-IgM, Ig heavy chain deletions, IgA deficiency, immunodeficiency with thymoma, reticular dysgenesis, Nezelof syndrome, selective IgG subclass deficiency, transient hypogammaglobulinemia of infancy, Wistcott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked severe combined immunodeficiency.

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

[73] 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.

[74] Other disease or disorders include, but not limited to, viral, genetic, allergic, and autoimmune diseases. Specific examples include, but not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary

inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft versus host disease, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythrematosus, ENL in leprosy, radiation damage, cancer, asthma, or hyperoxic alveolar injury.

[75] Examples of atherosclerosis and related conditions include, but are not limited to, those disclosed in U.S. patent 7,182,953, which is incorporated herein by reference. Specific examples include, but are not limited to, all forms of conditions involving atherosclerosis, including restenosis after vascular intervention such as angioplasty, stenting, atherectomy and grafting. All forms of vascular intervention are contemplated herein, including diseases of the cardiovascular and renal system, such as, but not limited to, renal angioplasty, percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA), carotid percutaneous transluminal angioplasty (PTA), coronary by-pass grafting, angioplasty with stent implantation, peripheral percutaneous transluminal intervention of the iliac, femoral or popliteal arteries, and surgical intervention using impregnated artificial grafts. The following chart provides a listing of the major systemic arteries that may be in need of treatment, all of which are contemplated herein:

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

[76] 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.

[77] 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.

[78] Examples of TNFα related disorders include, but are not limited to, those described in WO 98/03502 and WO 98/54170, both of which are incorporated herein in their entireties by reference. Specific examples include, but are not limited to: endotoxemia or toxic shock syndrome; cachexia; adult respiratory distress syndrome; bone resorption diseases such as arthritis; hypercalcemia; Graft versus Host Reaction; cerebral malaria; inflammation; tumor growth; chronic pulmonary inflammatory diseases; reperfusion injury; myocardial infarction; stroke; circulatory shock; rheumatoid arthritis; Crohn's disease; HIV infection and AIDS; other disorders such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis and other arthritic conditions, septic shock, septis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythromatosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS; disorders such as septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, oncogenic or cancerous conditions, asthma, autoimmune disease, radiation damages, and hyperoxic alveolar injury; viral infections, such as those caused by the herpes viruses; viral conjunctivitis; or atopic dermatitis.

[79] 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. Provisional Application No. 60/712,823, filed September 1, 2005, 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.

[80] Doses of a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer 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, or stereoisomer 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

[81] A compound provided herein, or a pharmaceutically acceptable salt, solvate, 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, or stereoisomer thereof, can also work to alleviate adverse effects associated with certain second active agents, and vice versa.

[82] 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).

[83] Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies. Specific examples of the active agents are anti-CD40 monoclonal antibodies (such as, for

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

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

[85] For instance, for the treatment, prevention or management of cancer, second active agents include, but are not limited to: semaxanib; cyclosporin; etanercept; doxycycline; bortezomib; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride;

ifosfamide; ilmofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

[86] Other second agents include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage

derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imatinib (Gleevec®), imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide;

nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (Genasense®); O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[87] Specific second active agents include, but are not limited to, 2-methoxyestradiol, telomestatin, inducers of apoptosis in mutiple myeloma cells (such as, for

example, TRAIL), statins, semaxanib, cyclosporin, etanercept, doxycycline, bortezomib, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatinum, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (*e.g.*, PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

[88] 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.

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

venlafaxine (Effexor®), trazodone (Desyrel®), bupropion (Wellbutrin®), mexiletine, nifedipine, propranolol, tramadol, lamotrigine, vioxx, ziconotide, ketamine, dextromethorphan, benzodiazepines, baclofen, tizanidine and phenoxybenzamine.

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

[91] 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.

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

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

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

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

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

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

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

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

[98] Examples of second active agent that may be used for the treatment, prevention and/or management of dysfunctional sleep and related syndromes include, but are not limited to, a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent (gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate), an antiaryhthmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, a second immunomodulatory compound, a combination agent, and other known or conventional agents used in sleep therapy. Specific examples include, but are not limited to, Neurontin, oxycontin, morphine, topiramate, amitryptiline, nortryptiline, carbamazepine, Levodopa, L-DOPA, cocaine, α-methyl-tyrosine, reserpine, tetrabenazine, benzotropine, pargyline, fenodolpam mesylate, cabergoline, pramipexole dihydrochloride, ropinorole, amantadine hydrochloride, selegiline hydrochloride, carbidopa, pergolide mesylate, Sinemet CR, Symmetrel, iproniazid,

clorgyline, phenelzine, isocarboxazid, tolcapone, entacapone, physostigmine saliclate, physostigmine sulfate, physostigmine bromide, meostigmine bromide, neostigmine methylsulfate, ambenonim chloride, edrophonium chloride, tacrine, pralidoxime chloride, obidoxime chloride, trimedoxime bromide, diacetyl monoxim, endrophonium, pyridostigmine, demecarium, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, RHo-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone, benzbromarone, betamethasone and other glucocorticoids, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and a mixture thereof.

[99] Examples of second active agents that may be used for the treatment, prevention and/or management of hemoglobinopathy and related disorders include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-I a, and interferon gamma-I b; and G-CSF; hydroxyurea; butyrates or butyrate derivatives; nitrous oxide; hydroxy urea; HEMOXIN™ (NIPRISAN™; *see* United States Patent No. 5,800,819); Gardos channel antagonists such as clotrimazole and triaryl methane derivatives; Deferoxamine; protein C; and transfusions of blood, or of a blood substitute such as Hemospan™ or Hemospan™ PS (Sangart).

[100] Administration of a compound provided herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer 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).

[101] 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.

[102] 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

[103] 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.

[104] 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.

[105] 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.

[106] 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.

[107] 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

[108] The pharmaceutical compositions provided herein contain therapeutically effective amounts of the compound of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, that is useful in the prevention, treatment, or amelioration of a disease described herein or one or more of the symptoms thereof.

[109] The compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, can be formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically, the compound of Formula I is formulated into pharmaceutical compositions using techniques and procedures well known in the art.

[110] In the compositions, effective concentrations of the compound of Formula I or pharmaceutically acceptable salt, solvate, hydrate is (are) mixed with a suitable pharmaceutical carrier or vehicle. The concentration of the compound in the compositions is effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases described herein.

[111] Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the

treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[112] In addition, the compound may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as known in the art. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

[113] The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compound in *in vitro* and *in vivo* systems described herein and then extrapolated therefrom for dosages for humans.

[114] The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of the diseases described herein.

[115] The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are

exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[116] Pharmaceutically acceptable derivatives include acids, bases, enol ethers and esters, salts, esters, hydrates, solvates forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

[117] Thus, effective concentrations or amounts of the compound described herein or a pharmaceutically acceptable derivative thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. The compound of Formula I is included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing diseases described herein. The concentration of the compound of Formula I in the composition will depend on absorption, inactivation, excretion rates of the compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

[118] The compositions are intended to be administered by a suitable route, including, but not limited to, orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets can be formulated. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration.

[119] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol, dimethyl acetamide or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[120] In instances in which the compound of formula I exhibit insufficient solubility, methods for solubilizing the compound may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate.

[121] Upon mixing or addition of the compound, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon

a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. In one embodiment, the effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[122] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compound or pharmaceutically acceptable derivatives thereof. The compound of Formula I and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refer to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the compound of Formula I sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

[123] Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the compound provided herein, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

[124] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example

pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain about 0.001%-100% active ingredient, in certain embodiments, about 0.1-85%, typically about 75-95%.

[125] The compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

[126] The compositions may include other active compounds to obtain desired combinations of properties. The compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

[127] Like the amounts and types of excipients, the amount the compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, 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 the compound of Formula I in an amount of from about 0.10 to about 500 mg. In other embodiments, dosage forms comprise the compound of Formula I 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. In one embodiment, dosage forms comprise the compound of Formula I in an amount of about 0.1, 0.2, 0.3. 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.25, 1.5, 1.75, 2, 2.25 or 2.5 mg. In another embodiment, dosage forms comprise the compound of Formula I in an amount of about 0.1 or 0.5 mg.

[128] 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 the compound of Formula I, and any optional additional active agents concurrently administered to the patient.

4.6.1 ORAL DOSAGE FORMS

[129] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

[130] In certain embodiments, the formulations are solid dosage forms, such as capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[131] Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[132] If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the

stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

[133] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compound, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[134] The compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

[135] Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[136] Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

[137] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are

non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

[138] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

[139] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is encapsulated in a gelatin capsule. For a liquid dosage form, the solution, e.g., for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be easily measured for administration.

[140] Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include, but are not limited to, those containing the compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether,

polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[141] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

[142] In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

[143] In one embodiment, the oral dosage form is a capsule comprising from about 0.1 mg to about 5 mg of the compound of Formula I. In one embodiment, the capsule comprises from about 0.1 to about 4 mg, about 0.1 to about 3 mg, about 0.1 to about 2.5 mg, about 0.1 to about 2 mg, about 0.1 to about 1 mg or about 0.1 to about 0.5 mg of the compound of Formula I. In one embodiment, oral dosage form is a capsule comprising about 0.1, 0.2, 0.25, 0.4, 0.5, 0.6, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5 mg of the compound of Formula I.

4.6.2 CONTROLLED RELEASE DOSAGE FORMS

[144] The compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, 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, 5,639,480, 5,733,566, 5,739,108, 5,891,474, 5,922,356, 5,972,891, 5,980,945, 5,993,855, 6,045,830, 6,087,324, 6,113,943, 6,197,350, 6,248,363, 6,264,970, 6,267,981, 6,376,461,6,419,961, 6,589,548, 6,613,358, 6,699,500 and 6,740,634, 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 ingredients provided herein.

[145] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed 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.

[146] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic 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 order to maintain this constant level of drug in the body, the drug must 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.

[147] In certain embodiments, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, *i.e.*, thus requiring only a fraction of the systemic dose. In some embodiments, a controlled release device is introduced into a subject in proximity of the site of inappropriate immune activation or a tumor. The active ingredient can be dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer

polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

4.6.3 PARENTERAL DOSAGE FORMS

[148] Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. In one embodiment, the composition is administered as an aqueous solution with hydroxypropyl-beta-cyclodextrin (HPBCD) as an excipient. In one embodiment, the aqueous solution contains about 1% to about 50% HPBCD. In one embodiment, the aqueous solution contains about 1%, 3%, 5%, 10% or about 20% HPBCD.

[149] Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained is also contemplated herein. Briefly, the compound of Formula I, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate

copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[150] Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[151] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[152] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[153] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone.

Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[154] The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

[155] The unit-dose parenteral preparations are packaged in an ampule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

[156] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[157] Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, such as more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

[158] The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

4.6.4 TOPICAL AND MUCOSAL DOSAGE FORMS

[159] 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,18th and 20th eds., Mack Publishing, Easton PA (1980, 1990 & 2000); 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.

[160] 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,18th and 20th eds., Mack Publishing, Easton PA (1980, 1990 & 2000).

[161] 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, or stereoisomers of the active ingredients can be used to further adjust the properties of the resulting composition.

4.6.5 KITS

[162] 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.

[163] In one embodiment, a kit comprises a dosage form of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. 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, ACE inhibitors, calcium channel blockers, proton pump inhibitors, NSAIDs, COX-inhibitors, corticosteroids, tetracycline, pentoxifylline, bucillamine, geranygeranyl transferase inhibitors, rotterlin, prolyl-4-hydroxylase inhibitors, c-proteinase inhibitors, lysyl-oxidase inhibitors, relaxin, halofuginone, prostaglandins, prostacyclins, endothelin-1, nitric oxide, angiotensin II inhibitors and anti-oxidants and those disclosed herein (*see, e.g.*, section 4.4).

[164] 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.

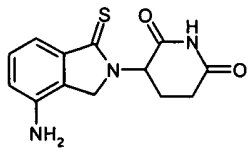
[165] Kits can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, 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

[166] Certain embodiments of the claimed subject matter are illustrated by the following non-limiting examples.

5.1 EXAMPLE 1

Preparation of 3-(4-Amino-1-thioxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione

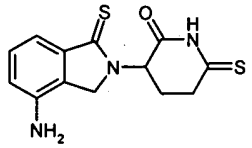


[167] A stirred suspension of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (1.5 g, 5.8 mmol) and Lawesson's reagent (1.3 g, 3.2 mmol) in 1,4-dioxane (150 mL) was heated to reflux for 15 hours. Reaction mixture was concentrated and residue was purified by chromatography (SiO_2, CH_2Cl_2 : EtOAc 3:7) to give 3-(4-amino-1-thioxo-1,3-dihydro-isoindol-2-yl)-piperiine-2,6-dione (0.64 g, 46%): mp 258-260°C; ^{1}H NMR (DMSO-d_6) δ 2.07-2.15 (m, 1H), 2.36-2.49 (m, 1H), 2.62-2.68 (m, 1H), 2.89-3.02 (m, 1H), 4.50 (d, J=20.1 Hz, 1H), 4.52 (d, J=20.1 Hz, 1H), 5.48 (s, 2H), 5.94-6.00 (dd, J=4.8 and 12.5 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 7.13 (d, J=7.5 Hz, 1H), 7.22 (t, J=7.5 Hz, 1H), 11.14 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.28, 31.04, 52.88, 55.47, 112.67, 116.57, 124.29, 129.04, 139.50, 143.16, 170.00, 172.57, 194.58; Anal. Calcd. for $C_{13}H_{13}N_3O_2S$ +0.2 H_2O: C, 55.98; H, 4.84; N, 15.06; S, 11.50. Found: C, 56.01; H, 4.65; N, 14.86; S, 11.65.

[168] In a similar fashion from 3-(5-amino-1-oxo-1,3-dihydroisoindol-2-yl)-piperidine-2,6-dione, 3-(6-amino-1-oxo-1,3-dihydroisoindol-2-yl)-piperidine-2,6-dione and 3-(4-amino-1,3-dioxo-1,3-dihydroisoindol-2-yl)-piperidine-2,6-dione, there is respectively obtained 3-(5-amino-1-thioxo-1,3-dihydro-isoindol-2-yl)-piperiine-2,6-dione, 3-(6-amino-1-thioxo-1,3-dihydro-isoindol-2-yl)-piperiine-2,6-dione and 3-(4-amino-1-thioxo-1,3-dihydro-isoindol-2-yl)-piperiine-2,6-dione.

5.2 EXAMPLE 2

Preparation of 3-(4-Amino-1-thioxo-1,3-dihydro-sioindol-2-yl)-6-thioxo-piperidin-2-one

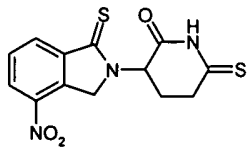


[169] A stirred suspension of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (1.5 g, 5.8 mmol) and Lawesson's reagent (2.3 g, 5.8 mmol) in 1,4-dioxane (110 mL) was refluxed for 5 hours. Reaction mixture was concentrated and residue was purified by chromatography (SiO_2, CH_2Cl_2 : EtOAc 3:7) to give 3-(4-amino-1-thioxo-1,3-dihydro-isoindolin-2-yl)-6-thioxo-piperidin-2-one (0.7 g, 43%): mp 182-184°C; ^{1}H NMR (DMSO-d_6) δ 2.09-2.17 (m, 1H), 2.48-2.53 (m, 1H), 3.24-3.39 (m, 2H), 4.52 (d, J=20.0 Hz, 1H), 4.54 (d, J=20.0 Hz, 1H), 5.48 (s, 2H), 5.99-6.05 (dd, J=4.4 and 12.5 Hz, 1H), 6.82-6.85 (dd, J=0.9 and 7.8 Hz, 1H), 7.11-7.14 (dd, J=0.8 and 7.5 Hz, 1H), 7.23 (t, J=6.0 Hz, 1H), 12.66 (s, 1H0; ^{13}C NMR (DMSO-d_6) δ 23.72, 40.81, 53.12, 55.58, 112.65,

116.62, 124.29, 129.08, 139.47, 143.16, 167.02, 194.48, 210.17; Anal. Calcd. For $C_{13}H_{13}N_3OS_2$ +0.3 H_2O : C, 52.61; H, 4.62; N, 14.16; S, 21.61. Found: C, 52.76; H, 4.43; N, 14.05; S, 21.20.

5.3 EXAMPLE 3

Preparation of 3-(4-Nitro-1-thioxo-1,3-dihydro-isoindol-2-yl)-6-thioxo-piperidin-2-one



[170] A stirred suspension of 3-(4-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-,6-dione (1.5 g, 5.2 mmol) and Lawesson's reagent (2.1 g, 5.2 mmol) in 1,4-dioxane (110 mL) was refluxed for 5 hours. Reaction mixture was concentrated and residue was purified by chromatography (SiO_2, CH_2Cl_2: EtOAc 9:1) to give 3-(4-nitro-1-thioxo-1,3-dihydro-isoindol-2-yl)-6-thioxo-piperidin-2-one (1.1 g, 64%) : mp 248-250°C; ^{1}H NMR (DMSO-d_6) δ 2.07-2.15 (m, 1H), 2.72-2.79 (m, 1H), 3.24-3.32 (m, 2H), 5.23 (d, J=21.8 Hz, 1H), 5.27 (d, J=21.8 Hz, 1H), 5.98-6.04 (dd, J=3.8 and 12.1 Hz, 1H), 7.86 (t, J=8.0 Hz, 1H), 8.30-8.33 (dd, J=0.8 and 7.7 Hz, 1H), 8.49-8.52 (dd, J=0.9 and 8.2 Hz, 1H), 12.67 (s, 1H); ^{13}C NMR (DMSO-d_6)δ 23.15, 40.78, 55.97, 56.42; 126.93, 130.27, 131.26, 136.17, 141.08, 143.12, 166.57, 190.81, 210.09; Anal. Calcd. For $C_{13}H_{11}N_3O_3S_2$: C, 48.59; H, 3.45; N, 13.07; S, 19.95. Found: C, 48.37; H, 3.34; N, 12.80; S, 19.73.

5.4 EXAMPLE 4

[171] Tablets, each containing 50 mg of 1,3-dithioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline, can be prepared in the following manner:

Constituents (for 1000 tablets)	
1,3-dithioxo-2-(2,6-dioxo-piperidin-3-yl) -5-amino- isoindoline	50.0 g
lactose	50.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralized water	q.s

[172] The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, talc, magnesium stearate and half of the starch then are

mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 mL of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35 °C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

5.5 EXAMPLE 5

[173] Tablets, each containing 100 mg of 1,3-dithioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline, can be prepared in the following manner:

Constituents (for 1000 tablets)	
1,3-dithioxo-2-(2,6-dioxo-piperidin-3-yl) -5-amino- isoindoline	100.0 g
lactose	100 g
wheat starch	47.0 g
magnesium stearate	3.0 g
demineralized water	q.s

[174] All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35 °C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

5.6 EXAMPLE 6

[175] Tablets for chewing, each containing 75 mg of 1-thioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline, can be prepared in the following manner:

Constituents (for 1000 tablets)	
1,3-thioxo-2-(2,6-dioxo-piperidin-3-yl) -5-amino- isoindoline	75.0 g
mannitol	230.0 g
lactose	150 g
talc	21.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.5 g
gelatin solution	gelatin solution

[176] All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50 °C and again forced through a sieve of 1.7 mm mesh width. 1-Thioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

5.7 EXAMPLE 7

[177] Tablets, each containing 10 mg of 1-thioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline, can be prepared in the following manner:

Constituents (for 1000 tablets)	
1-thioxo-2-(2,6-dioxo-piperidin-3-yl) -5-amino- isoindoline	10.0 g
lactose	328.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
magnesium stearate	4.0 g
demineralized water	q.s

[178] The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35 °C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

5.8 EXAMPLE 8

[179] Gelatin dry-filled capsules, each containing 100 mg of 1-thioxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline, can be prepared in the following manner:

Constituents (for 1000 capsules)	
1-thioxo-2-(2,6-dioxo-piperidin-3-yl) -6-amino- isoindoline	10.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

[180] The sodium lauryl sulfate is sieved into the 1-thioxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

5.9 EXAMPLE 9

[181] A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

1-thioxo-2-(2,6-dioxo-piperidin-3-yl) -7-amino- isoindoline	5.0 g
sodium chloride	22.5 g
phosphate buffer pH 7.4	300.0 g
demineralized water to	2500.0 mL

[182] 1-Thioxo-2-(2,6-dioxopiperidin-3-yl)-7-aminoisoindoline is dissolved in 1000 mL of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 mL with water. To prepare dosage unit forms, portions of 1.0 or 2.5 mL each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of imide).

5.10 EXAMPLE 10

5.10.1 TNFα Inhibition Assay in PMBC

[183] Peripheral blood mononuclear cells (PBMC) from normal donors are obtained by Ficoll Hypaque (Pharmacia, Piscataway, NJ, USA) density centrifugation. Cells are cultured in RPMI 1640 (Life Technologies, Grand Island, NY, USA) supplemented with 10% AB+human serum (Gemini Bio-products, Woodland, CA, USA), 2 mM L-glutamine, 100 U/ml penicillin, and 100 g/ml streptomycin (Life Technologies).

[184] PBMC (2 x 10^5 cells) are plated in 96-well flat-bottom Costar tissue culture plates (Corning, NY, USA) in triplicate. Cells are stimulated with LPS (from Salmonella abortus equi, Sigma cat.no. L-1887, St.Louis, MO, USA) at 1 ng/ml final in the absence or presence of compounds. Compounds provided herein are dissolved in DMSO (Sigma) and further dilutions are done in culture medium immediately before use. The final DMSO concentration in all assays can be about 0.25%. Compounds are added to cells 1 hour before LPS stimulation. Cells are then incubated for 18-20 hours at 37°C in 5 % CO_2, and supernatants are then collected, diluted with culture medium and assayed for TNF levels by

ELISA (Endogen, Boston, MA, USA). IC_{50}s are calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100% and bottom to 0%, allowing variable slope (GraphPad Prism v3.02).

5.10.2 IL-2 and MIP-3α Production by T Cells

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

[186] Tissue culture 96-well flat-bottom plates are coated with anti-CD3 antibody OKT3 at 5 μg/ml in PBS, 100 μl per well, incubated at 37°C for 3-6 hours, then washed four times with complete medium 100 μl/well just before T cells are added. Compounds are diluted to 20 times of final in a round bottom tissue culture 96-well plate. Final concentrations are about 10 μM to about 0.00064 μM. A 10 mM stock of compounds provided herein is diluted 1:50 in complete for the first 20x dilution of 200 μM in 2 % DMSO and serially diluted 1:5 into 2 % DMSO. Compound is added at 10 μl per 200 l culture, to give a final DMSO concentration of 0.1 %. Cultures are incubated at 37°C, 5 % CO_2 for 2-3 days, and supernatants analyzed for IL-2 and MIP-3 by ELISA (R&D Systems). IL-2 and MIP-3 levels are normalized to the amount produced in the presence of an amount of a compound provided herein, and EC_{50}s calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope (GraphPad Prism v3.02).

5.10.3 Cell Proliferation Assay

[187] Cell lines Namalwa, MUTZ-5, and UT-7 are obtained from the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (Braunschweig, Germany). The cell line KG-1 is obtained from the American Type Culture Collection (Manassas, VA, USA). Cell proliferation as indicated by ^{3}H-thymidine incorporation is measured in all cell lines as follows.

[188] Cells are plated in 96-well plates at 6000 cells per well in media. The cells are pre-treated with compounds at about 100, 10, 1, 0.1, 0.01, 0.001, 0.0001 and 0 M in a final concentration of about 0.25 % DMSO in triplicate at 37°C in a humidified incubator at 5 % CO_2 for 72 hours. One microcurie of ^{3}H-thymidine (Amersham) is then added to each well, and cells are incubated again at 37C in a humidified incubator at 5 % CO_2 for 6 hours. The cells are harvested onto UniFilter GF/C filter plates (Perkin Elmer) using a cell harvester (Tomtec), and the plates are allowed to dry overnight. Microscint 20 (Packard) (25 ÿl/well) is added, and plates are analyzed in TopCount NXT (Packard). Each well is counted for one minute. Percent inhibition of cell proliferation is calculated by averaging all triplicates and normalizing to the DMSO control (0 % inhibition). Each compound is tested in each cell line in three separate experiments. Final IC_{50}s are calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope. (GraphPad Prism v3.02).

5.11 EXAMPLE 11

[189] Certain compouds provided herein, i.e., **3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(4-amino-1-thioxo-1,3-dihydroisoindol-2-yl)-6-thioxo-piperidin-2-one, and 3-(4-nitro-1-thioxo-1,3-dihydroisoindol-2-yl)-6-thioxo-piperidin-2-one, were tested for their abilities to inhibit TNFα and proliferation of Namalwa cells and to stimulate IL-2, following the procedures substantially similar those described in Section 5.10, above. All of the tested compounds showed activities in the ranges of μM-mM.**

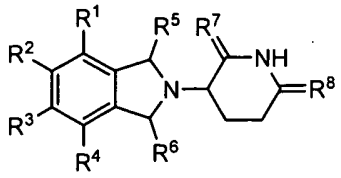
[190] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the claimed subject matter and are encompassed by the appended claims.

[191] All of the patents, patent applications and publications referred to herein are incorporated herein in their entireties. Citation or identification of any reference in this application is not an admission that such reference is available as prior art. The full scope of the claimed subject matter is better understood with reference to the appended claims.

CLAIMS

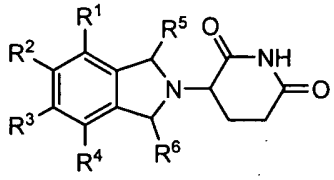
What is claimed is:

1. A compound of formula (I)



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of R^1-R^4 is NH_2 or NO_2, and the others of R^1-R^4 are each hydrogen; R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo; and R^7 and R^8 are each independently thioxo or oxo.

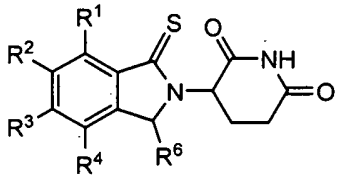
2. The compound of claim 1, wherein the compound has formula (II):



(II)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of R^1-R^4 is NH_2, and the others of R^1-R^4 are each hydrogen; and R^5 and R^6 are each independently thioxo or hydrogen, provided that at least one of R^5 or R^6 is thioxo.

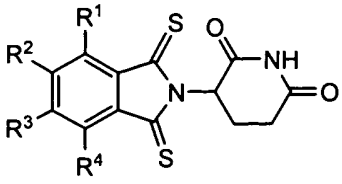
3. The compound of claim 1 having formula (III)



(III)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

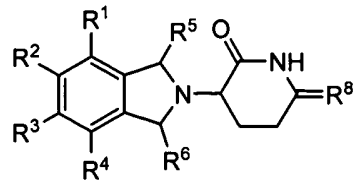
4. The compound of claim 1 having formula (IV)



(IV)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

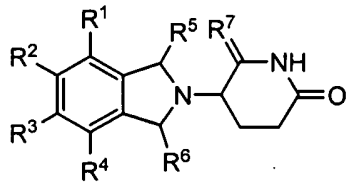
5. The compound of claim 1 having formula (V)



(V)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

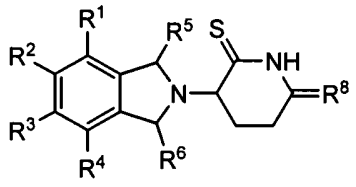
6. The compound of claim 1 having formula (VI)



(VI)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

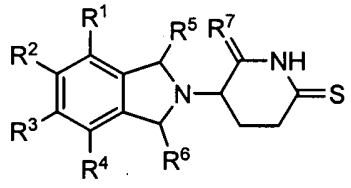
7. The compound of claim 1 having formula (VII)



(VII)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

8. The compound of claim 1 having formula (VIII)



(VIII)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

9. The compound of claim 1, which is 3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione or 3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione.

10. The compound of claim 1, which is 3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or 3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione.

11. The compound of claim 1, which is (R)-3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione or (R)-3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione.

12. The compound of claim 1, which is (S)-3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione or (S)-3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione.

13. The compound of claim 1, which is (R)-3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (R)-3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (R)-

3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or (R)-3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione.

14. The compound of claim 1, which is (S)-3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (S)-3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (S)-3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or (S)-3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione.

15. The compound of claim 1, which is 3-(4-amino-1-thioxo-1,3-dihydro-isoindol-2-yl)-6-thioxo-piperidin-2-one or 3-(4-nitro-1-thioxo-1,3-dihydro-isoindol-2-yl)-6-thioxo-piperidin-2-one.

16. A pharmaceutical composition comprising a compound of claim 1, or a salt or optical isomer thereof and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, wherein the compound is 3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione or 3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione.

18. The pharmaceutical composition of claim 16, wherein the compound is 3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, 3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or 3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione.

19. The pharmaceutical composition of claim 16, wherein the compound is (R)-3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione or (R)-3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione.

20. The pharmaceutical composition of claim 16, wherein the compound is (S)-3-(4-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione or (S)-3-(5-amino-1,3-dithioxoisoindolin-2-yl)piperidine-2,6-dione.

21. The pharmaceutical composition of claim 16, wherein the compound is (R)-3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (R)-3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (R)-3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or (R)-3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione.

22. The pharmaceutical composition of claim 16, wherein the compound is (S)-3-(4-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (S)-3-(5-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione, (S)-3-(6-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione or (S)-3-(7-amino-1-thioxoisoindolin-2-yl)piperidine-2,6-dione.

23. The pharmaceutical composition of claim 16, which is 3-(4-amino-1-thioxo-1,3-dihydro-isoindol-2-yl)-6-thioxo-piperidin-2-one or 3-(4-nitro-1-thioxo-1,3-dihydro-isoindol-2-yl)-6-thioxo-piperidin-2-one.

24. A method of treating, managing or preventing a disease or disorder comprising administering to a patient a compound of any of claims 1-15, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the disease or disorder is cancer, a disorder associated with angiogenesis, pain, macular degeneration or a related syndrome, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis or a related disorder, dysfunctional sleep or a related disorder, hemoglobinopathy or a related disorder, or a TNFα related disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/002980

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4035 A61P29/00 A61P35/00 A61P25/28 C07D401/04

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 A61P A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/028436 A (GOVERNMENT OF UNITED STATES OF [US]; GREIG NIGEL H [US]; HOLLOWAY HARO) 31 March 2005 (2005-03-31) pages 12,22 page 42; example 11; compounds 212, 215, 216 claims 1,5,8,54-56 page 49; table 1	1-24
Y	MULLER G W ET AL: "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 9, no. 11, 7 June 1999 (1999-06-07), pages 1625-1630, XP004169632 ISSN: 0960-894X page 1627; compounds 4,5	1-24

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 October 2009	14/10/2009

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	Lewis, Sara

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/002980

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/03502 A (CELGENE CORP [US]; MULLER GEORGE W [US]; STIRLING DAVID I [US]; CHEN R) 29 January 1998 (1998-01-29) page 13 - page 14; examples 1,2	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/002980

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