4'-O-SUBSTITUTED ISOINDOLINE DERIVATIVES AND COMPOSITIONS COMPRISING AND METHODS OF USING THE SAME

[1] This application claims priority to U.S. Provisional Application No. 60/919,323, filed March 20, 2007, entitled "4'-O-Substituted Isoindoline Derivatives And Compositions Comprising And Methods Of Using The Same", to Ruchelman *et al.*, the entirety of which is incorporated herein by reference.

1. FIELD

[2] Provided herein are 4'-O-substituted isoindoline derivatives. Pharmaceutical compositions comprising the compounds and methods for treating, preventing and managing various disorders using the compounds and compositions are also disclosed.

2. BACKGROUND

2.1 PATHOBIOLOGY OF CANCER AND OTHER DISEASES

[3] 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).

[4] 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.

[5] 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).

[6] 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.

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

2.2 METHODS OF TREATING CANCER

[8] 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.

[9] 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.

[10] 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).

[11] 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.

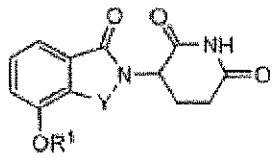
[12] Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, hepain and steroids have been proposed to be useful in the treatment of certain specific diseases. Taylor *et al.*, *Nature* 297:307 (1982);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

[13] 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

[14] Provided herein are 4'-O-substituted isoindoline compounds, and pharmaceutically acceptable salts, solvates (*e.g.*, hydrates), prodrugs, clathrates, or stereoisomers thereof.

[14a] In a first aspect, there is provided a compound of formula:



a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof, wherein:

Y is CH_2; and

R^1 is heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl or heterocyclylcarbonyl;

and where R^1 is optionally substituted with one or more groups selected from alkoxy, halo, alkyl, carboxy, alkylaminocarbonyl, alkoxycarbonyl, nitro, amine, nitrile, haloalkyl, hydroxy, and alkylsulfonyl.

[14b] In a second aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[15] Also provided are methods of treating and managing various diseases or disorders. The methods comprise administering to a patient in need of such treatment or

management a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof.

[16] Further provided are methods of preventing various diseases and disorders, which comprise administering to a patient in need of such prevention a prophylactically effective amount of a compound provided herein, or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof.

[17] 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, prodrug, clathrate, or stereoisomer thereof.

[17a] In a third aspect, there is provided a single unit dosage form comprising a compound as defined above, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

4. DETAILED DESCRIPTION

[18] In one embodiment, provided are isoindoline compounds, and pharmaceutically acceptable salts, solvates, prodrugs, clathrate, and stereoisomers thereof.

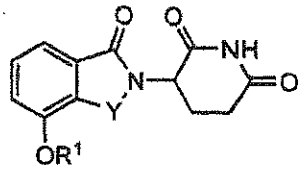
[19] In another embodiment, provided are methods of treating, managing, and preventing various diseases and disorders, which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a compound provided herein, or a pharmaceutically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

[20] In other embodiments, a compound provided herein, or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, 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.

[21] 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, prodrug, clathrate, or stereoisomer thereof, and optionally a second active agent.

4.1 COMPOUNDS

[22] In one embodiment, the compounds provided herein for use in the pharmaceutical compositions and methods have formula I:



, I

or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof, wherein Y is C=O or CH_2, and R^1 is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, arylaminocarbonyl, alkylcarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl or heterocyclylcarbonyl; where R^1 is optionally substituted with one or more, in certain embodiments, 1, 2, 3 or 4 substituents, one, two or three groups selected from alkoxy, halo, alkyl, carboxy, alkylaminocarbonyl, alkoxycarbonyl, nitro, amine, nitrile, haloalkyl, hydroxy, and alkylsulfonyl.

[23] In one embodiment, Y is C=O. In another embodiment, Y is CH_2.

[24] In certain embodiments, R^1 is alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, optionally substituted with one or more, in one embodiment, one, two or three groups selected from alkoxy, halo, alkyl and alkylsulfonyl. In one embodiment, R^1 is aryl, aralkyl or heteroarylalkyl. In certain embodiments, the aryl or heteroaryl ring in group R^1 is a 5 or 6 membered monocyclic ring. In certain embodiments, the heteroaryl ring in R^1 group is a 5 or 6 membered monocyclic ring containing 1-3 heteroatoms selected from O, N and S. In certain embodiments, the aryl or heteroaryl ring in group R^1 is a bicyclic ring. In certain embodiments, the heteroaryl ring contains 1-3 heteroatoms selected from O, N and S and is attached to the alkyl group via a hetero atom in the ring. In certain embodiments, the heteroaryl ring is attached to the alkyl group via a carbon atom in the ring.

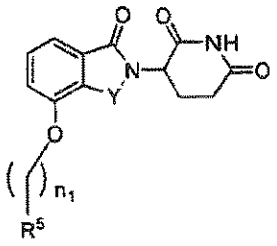
[25] In one embodiment, R^1 is phenyl, benzyl, naphthylmethyl, quinolylmethyl, benzofurylmethyl, benzothienylmethyl, furylmethyl or thienylmethyl, optionally substituted with one or more, in one embodiment, one, two or three groups selected from alkoxy, halo, alkyl and alkylsulfonyl. In one embodiment, R^1 is optionally substituted with one or two substituents selected from methoxy, chloro, bromo, fluoro, methyl and methylsulfonyl.

[26] In other embodiments, R^1 is 2-methoxyphenyl, benzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3,4-dichlorobenzyl, 3,5-dichlorobenzyl, 3-fluorobenzyl, 3-bromobenzyl, 3-methylbenzyl, 4-methylsulfonylbenzyl, 3-methoxybenzyl, naphthylmethyl, 3-

quinolylmethyl, 2-quinolylmethyl, 2-benzofurylmethyl, 2-benzothienylmethyl, 3-chlorothien-2-ylmethyl, 4-fluorobenzothien-2-ylmethyl, 2-furylmethyl, 5-chlorothien-2-ylmethyl or 1-naphth-2-ylethyl.

[27] In one embodiment, R^1 is heterocyclyl. In certain embodiments, the heterocyclyl ring in R^1 group is a 5 or 6 membered monocyclic ring containing 1-3 heteroatoms selected from O, N and S. In certain embodiments, the heterocyclyl ring in group R^1 is piperidinyl or tetrahydropyranyl.

[28] In certain embodiments, the compounds have formula II:



, II

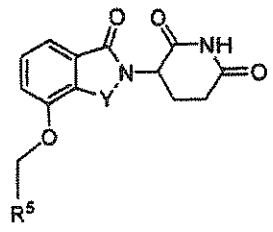
[29] wherein Y is C=O or CH_2, and R^5 is aryl or heteroaryl, optionally substituted with one, two or three groups seleted from alkyl, halo, alkoxy, carboxy, alkylaminocarbonyl, alkoxycarbonyl, nitro, amine, nitrile, haloalkyl, hydroxy, and alkylsulfonyl; n_1 is 0-5, and the other variables are as described elsewhere herein.

[30] In one embodiment, Y is C=O. In another embodiment, Y is CH_2.

[31] In one embodiment, n_1 is 0 or 1. In certain embodiments, R^5 is selected from phenyl, naphthyl, furyl, thienyl, benzofuryl, benzothienyl and quinolyl, optionally substituted with one or two groups selected from methyl, methoxy, chloro, fluoro, bromo and methylsulfonyl. In other embodiments, R^5 is phenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-fluorophenyl, 3-bromophenyl, 3-methylphenyl, 4-methylsulfonylphenyl, 3-methoxyphenyl, naphthyl, 3-quinolyl, 2-quinolyl, 2-benzofuryl, 2-benzothienyl, 3-chlorothien-2-yl, 4-fluorobenzothien-2-yl, 2-furyl, 5-chlorothien-2-yl or 1-naphth-2-yl.

[32] In one embodiment, n_1 is 0 or 1. In certain embodiments, R^5 is selected from phenyl, benzyl, naphthyl, furyl, thienyl, benzofuryl, benzothienyl and quinolyl, optionally substituted with one or two groups selected from methyl, methoxy, chloro, fluoro, bromo and methylsulfonyl.

[33] In one embodiment, the compounds have formula III

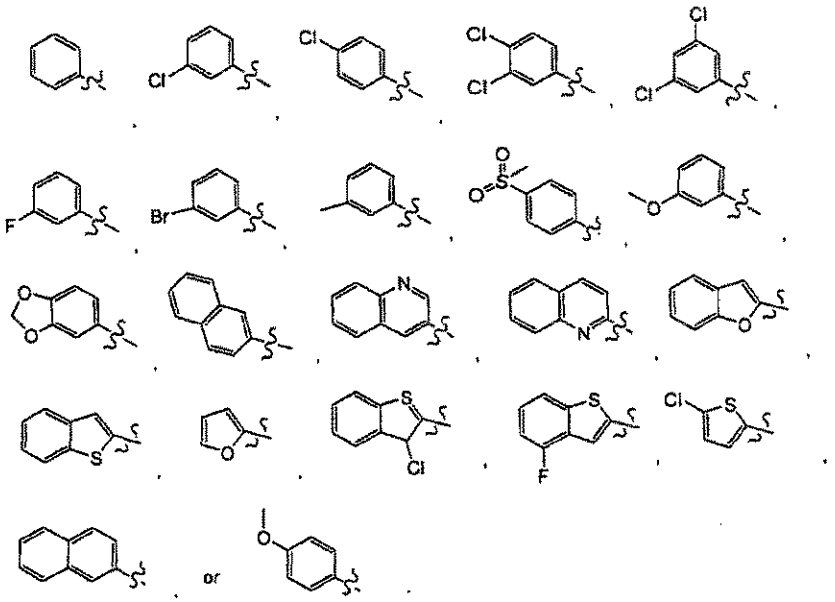


, III

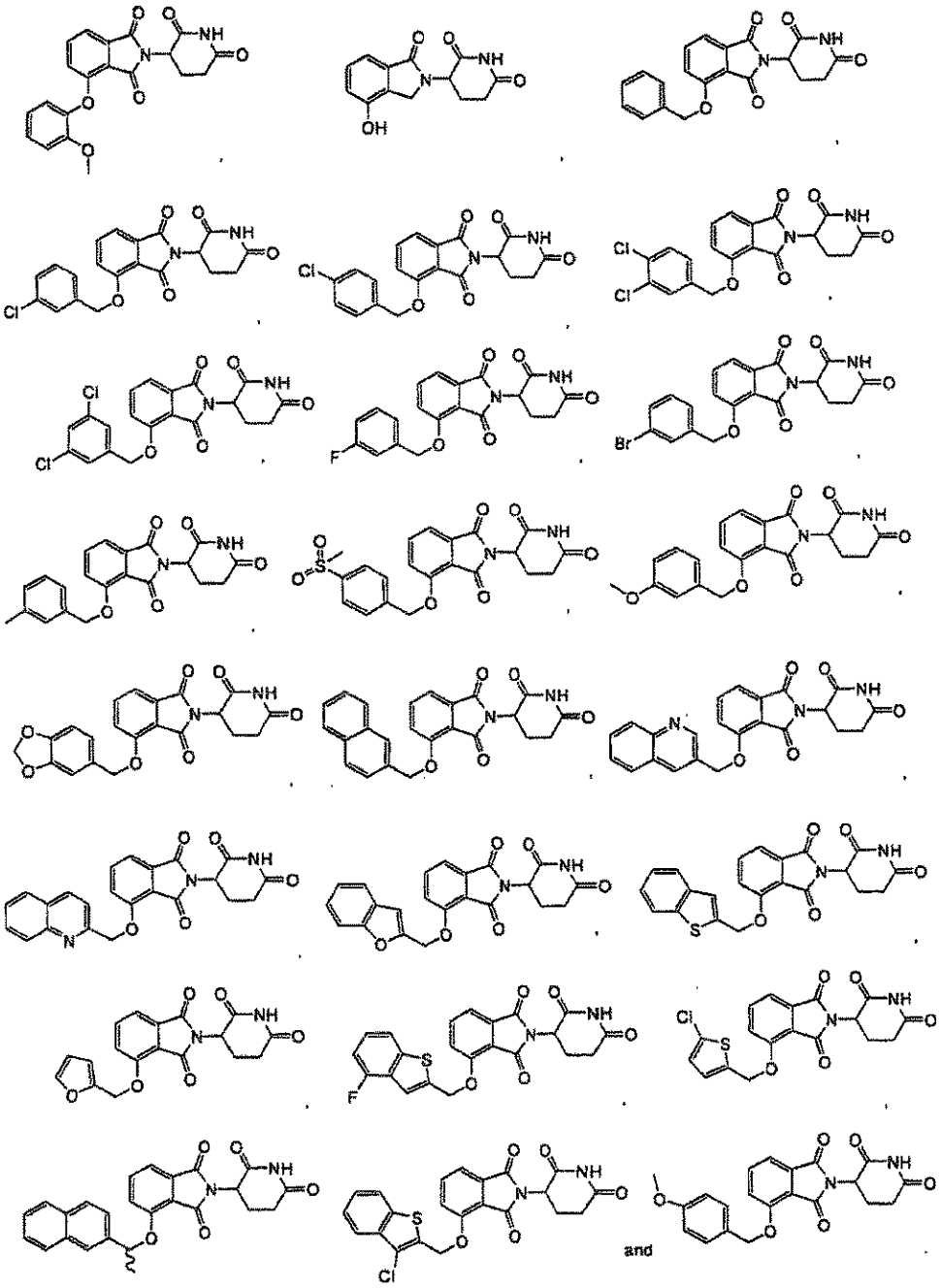
wherein the variables are as described elsewhere herein.

[34] In one embodiment, Y is C=O. In another embodiment, Y is CH_2.

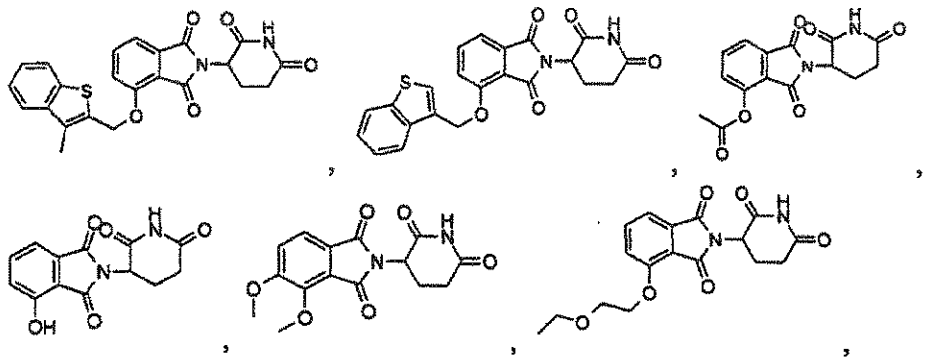
[35] In one embodiment, R^5 is

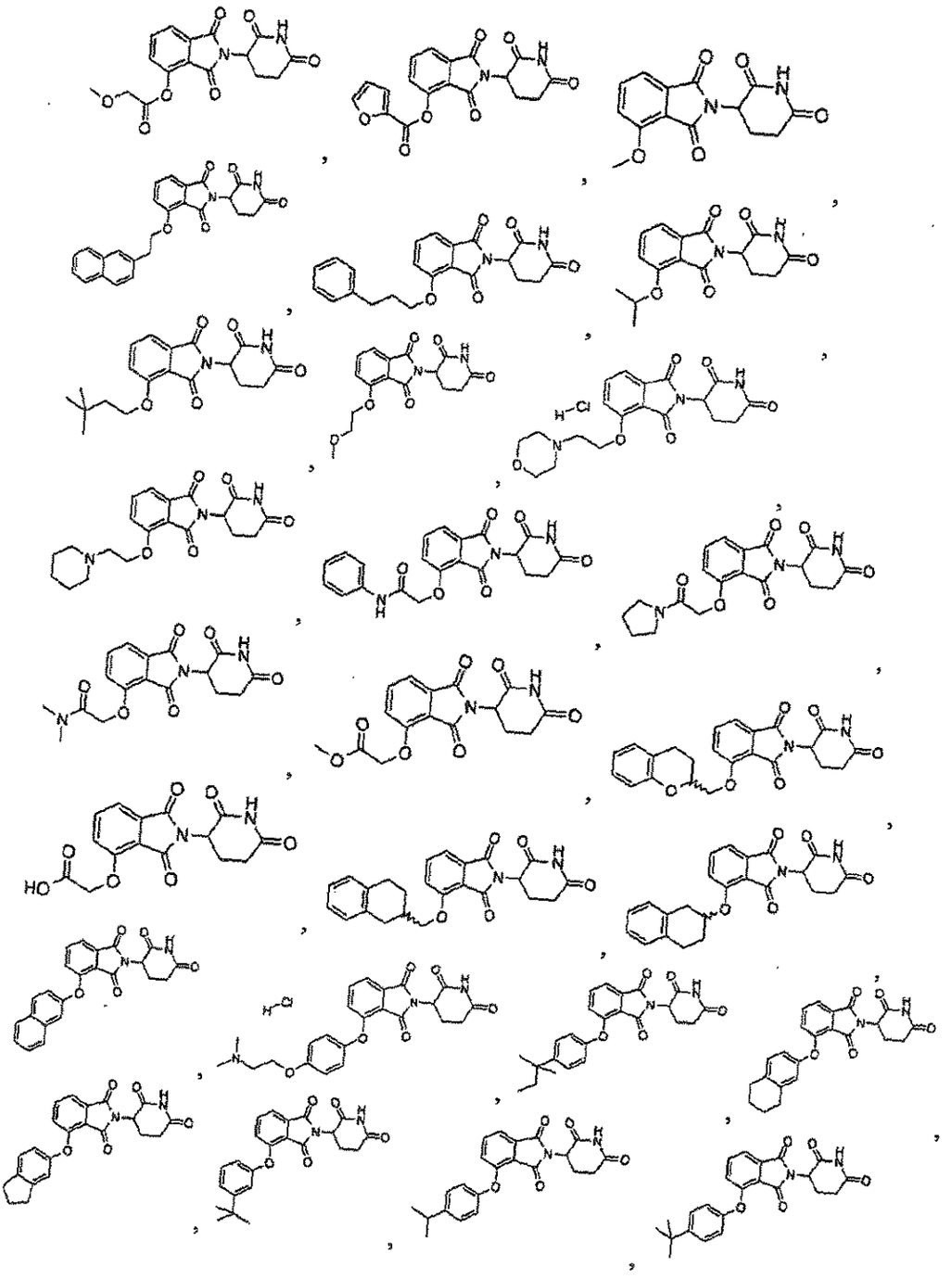


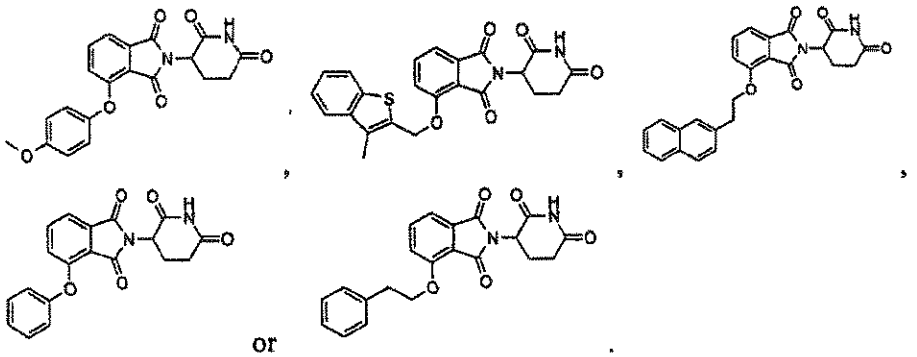
[36] Examples include, but are not limited to, those listed below, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), prodrug, clathrate, or stereoisomer thereof:



[37] In certain embodiments, the compound is:

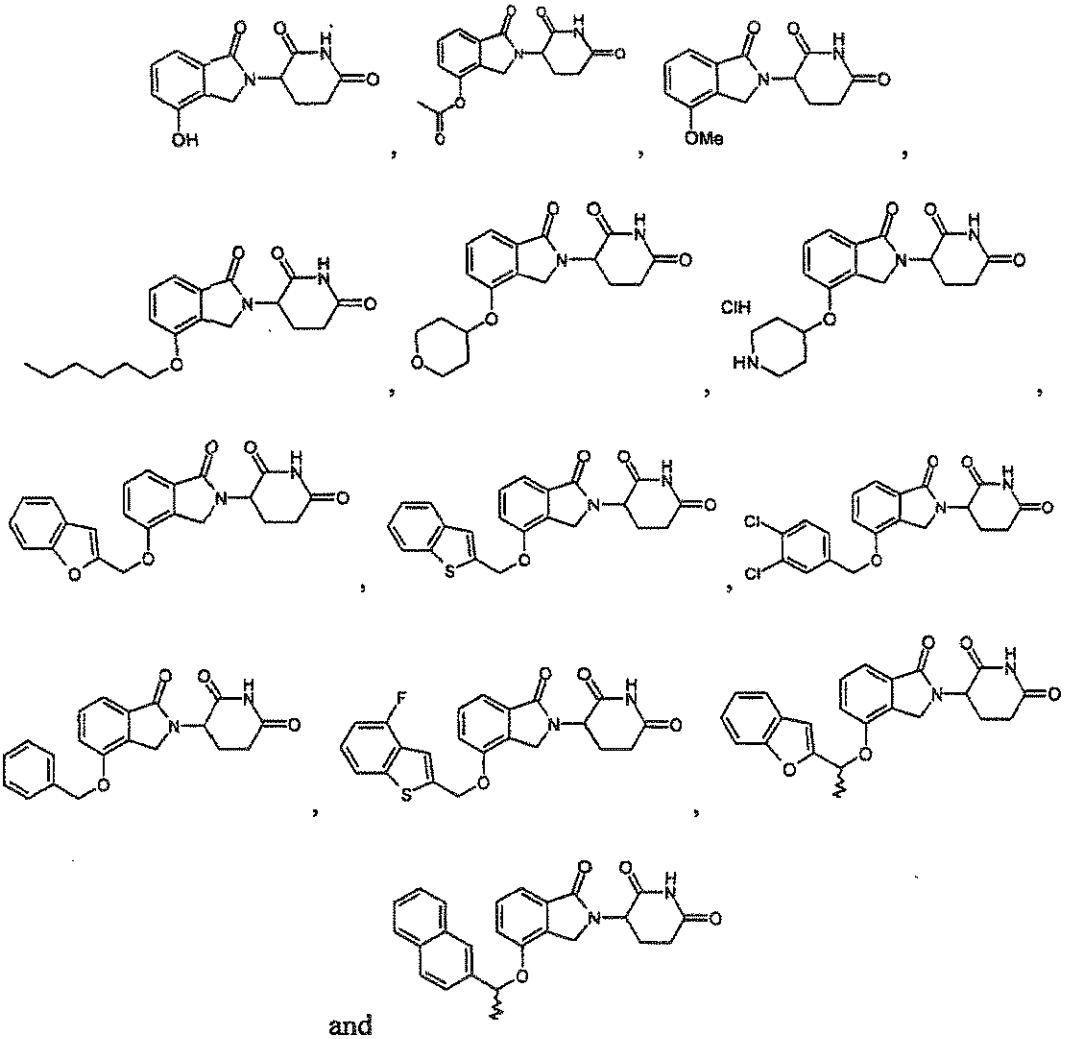






or

[38] In one embodiment, the compound is selected from



and

[39] 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, glucuronic, 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. In one embodiment, suitable are hydrochloric, hydrobromic, phosphoric, and sulfuric acids.

[40] 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.

[41] As used herein, and unless otherwise specified, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide the compound. Examples of prodrugs include, but are not limited to, compounds that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include compounds that comprise -NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elselvier, New York 1985).

[42] As used herein, and unless otherwise specified, the terms "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide" and "biohydrolyzable phosphate " mean a carbamate, carbonate, ureide and phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted *in vivo* to the biologically active compound. Examples of biohydrolyzable carbamates include, but are not limited to, carbamates that include lower alkylamine, substituted ethylenediamine, aminoacid, hydroxyalkylamine, heterocyclic and heteroaromatic amine, and polyether amine moieties.

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

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

[45] 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.

[46] 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.

[47] As used herein, and unless otherwise indicated, the term "alkyl" refers to a saturated straight chain or branched hydrocarbon having a number of carbon atoms as specified herein. In some embodiments, alkyl groups have 1 to 15, 1 to 10, 1 to 6, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-

methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The term "alkyl" also encompasses cycloalkyl.

[48] As used herein, alkenyl refers to a straight chain or branched hydrocarbon containing one or more double bonds. Exemplary alkenyl carbon chains contain from 2 to 20 carbons, and in certain embodiments, contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds.

[49] As used herein, alkynyl refers to a straight chain or branched hydrocarbon containing one or more triple bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkenyl and alkynyl groups herein include, but are not limited to, ethene, propene, butene, pentene, acetylene and hexyne. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 6 carbons.

[50] As used herein, and unless otherwise specified, the term "cycloalkyl" means a specie of alkyl, which is cyclic and contains from 3 to 15, 3 to 9, 3 to 6, or 3 to 5 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Examples of unsubstituted cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and adamantyl. A cycloalkyl may be substituted with one or more substituents. In some embodiments, a cycloalkyl may be a cycloalkyl fused with aryl or heteroaryl groups.

[51] As used hereinm and unless otherwise specified, the term "heterocycloalkyl" means a cycloalkyl in which one or more carbon atoms are replaced by heteroatoms such as, but not limited to, N, S, and O. In some embodiments, a heterocycloalkyl group contains contains from 2 to 14, 2 to 8, 2 to 7, 2 to 5, or 2 to 4 carbon atoms. In some embodiments, a heterocycloalkyl may be a heterocycloalkyl fused with aryl or heteroaryl groups.

[52] As used herein, the term "aryl" means a carbocyclic aromatic ring containing from 5 to 14 ring atoms. The ring atoms of a carbocyclic aryl group are all carbon atoms. Aryl ring structures include compounds having one or more ring structures such as mono-, bi-, or tricyclic compounds as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl and the like. Specifically, the aryl group may be a mono- , bi-, or tricyclic ring. Representative aryl groups include phenyl, anthracenyl, fluorenyl, indenyl, azulenyl, phenanthrenyl and naphthyl.

[53] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in

one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, indolinyl, pyrrolidinyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl.

[54] As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, acyl, guanidino, or the nitrogen may be quaternized to form an ammonium group where the substituents are selected as above.

[55] As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

[56] As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

[57] As used herein, "alkylaminocarbonyl" refers to C(O)NHR in which R is alkyl, including lower alkyl. As used herein, "dialkylaminocarbonyl" refers to C(O)NR'R in which R' and R are independently alkyl, including lower alkyl; "carboxamide" refers to groups of formula -NR'COR in which R' and R are independently alkyl, including lower alkyl.

[58] As used herein, "arylaminocarbonyl" refers to -C(O)NHR in which R is aryl, including lower aryl, such as phenyl.

[59] As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

[60] Where the number of any given substituent is not specified (e.g., "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

[61] It should be noted that if there is a discrepancy between a depicted structure and a name given to 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.

4.2 METHODS OF TREATMENT, PREVENTION AND MANAGEMENT

[62] Provided herein are methods of treating, preventing, and/or managing various diseases or disorders using a compound provided herein, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), prodrug, clathrate, or stereoisomer thereof.

[63] 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.

[64] 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.

[65] As used herein, unless otherwise specified, the term "preventing" refers to the treatment with or administration of a compound provided herein, with or without other additional active compound, prior to the onset of symptoms, particularly to patients at risk of cancer and/or other disorders described herein. The term "prevention" includes the inhibition or reduction of a symptom of the particular disease. Patients with familial history of a disease in particular are candidates for preventive regimens in certain embodiments. In addition, patients who have a history of recurring symptoms are also potential candidates for the prevention. In this regard, the term "prevention" may be interchangeably used with the term "prophylactic treatment."

[66] 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.

[67] 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.

[68] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to inhibit or reduce a symptom of a disease or to prevent recurrence of a disease. 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 inhibition or reduction of a symptom of a disease or recurrence of a disease. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

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

[70] 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.

[71] 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, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation.

[72] 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.

[73] 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.

[74] 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).

[75] 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.

[76] 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.

[77] 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.

[78] 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.

[79] 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).

[80] 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).

[81] 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.

[82] 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.

[83] 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).

[84] 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.

[85] 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.

[86] 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.

[87] 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.

[88] 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.

[89] 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.

[90] 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.

[91] Examples of atherosclerosis and related conditions include, but are not limited to, those disclosed in U.S. publication no. 2002/0054899, published May 9, 2002, which is incorporated herein by reference. Specific examples include, but are not limited to, all forms of conditions involving atherosclerosis, including restenosis after vascular intervention such as angioplasty, stenting, atherectomy and grafting. All forms of vascular intervention are contemplated herein, including diseases of the cardiovascular and renal system, such as, but not limited to, renal angioplasty, percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA), carotid percutaneous transluminal angioplasty (PTA), coronary by-pass grafting, angioplasty with stent implantation, peripheral percutaneous transluminal intervention of the iliac, femoral or

popliteal arteries, and surgical intervention using impregnated artificial grafts. The following chart provides a listing of the major systemic arteries that may be in need of treatment, all of which are contemplated herein:

Table 1

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
Left gastric	muscles, uterus and vagina
Middle sacral	Esophagus and stomach
Ovarian	Sacrum
Palmar arch	Ovaries
Peroneal	Hand
Popliteal	Calf
Posterior tibial	Knee
Pulmonary	Calf
Radial	Lungs
Renal	Forearm
Splenic	Kidney
Subclavian	Stomach, pancreas, and spleen
Superior mesenteric	Shoulder
Testicular	Pancreas, small intestine, ascending and transverse colon
Ulnar	Testes
	Forearm

[92] 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.

[93] 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.

[94] 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.

[95] In other embodiments, the use of compounds provided herein in various immunological applications, *i.e.*, use of compounds provided herein in combination with a vaccination, for example, as vaccine adjuvant. Although any methods and manners of use of compounds provided herein in combination with a vaccine are contemplated herein, a non-limiting example of such uses is the use of compounds provided herein as vaccine adjuvants, according to the administration regimens disclosed in U.S. Provisional Application No. 60/712,823, filed September 1, 2005, which is incorporated herein in its entirety by reference. 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 compounds provided herein, such as, but not limited to, reduction or desensitization of allergic reactions.

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

4.3 SECOND ACTIVE AGENTS

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

[98] 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).

[99] 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).

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

[101] For instance, for the treatment, prevention or management of cancer, second active agents include, but are not limited to: semaxanib; cyclosporin; etanercept; doxycycline; bortezomib; lapatinib (Tykerb®); 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.

[102] 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; chlorins; 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.

[103] 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.

[104] 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.

[105] 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.

[106] 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.

[107] 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.

[108] Examples of second active agents that may be used for the treatment, prevention and/or management of pulmonary hypertension and related disorders include, but are not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelin antagonists, phosphodiesterase inhibitors (e.g., PDE V inhibitors), endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors, and other therapeutics known to reduce pulmonary artery pressure. Specific examples include, but are not limited to, warfarin (Coumadin®), a diuretic, a cardiac glycoside, digoxin-oxygen, diltiazem, nifedipine, a vasodilator such as prostacyclin (*e.g.*, prostaglandin 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®).

[109] 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.

[110] 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 stibogluconate), interfereon gamma, itraconazole, a combination of dead promastigotes and BCG, leucovorin, corticosteroids, sulfonamide, spiramycin, IgG (serology), trimethoprim, and sulfamethoxazole.

[111] 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).

[112] 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.

[113] 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.

[114] 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.

[115] 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).

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

[117] 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.

[118] 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.

4.4 Cycling Therapy

[119] 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.

[120] 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.

[121] 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.

[122] 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.

[123] 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.

4.5 PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[124] Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms provided herein comprise a compound provided herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms can further comprise one or more excipients.

[125] Pharmaceutical compositions and dosage forms provided herein can also comprise one or more additional active ingredients. Examples of optional second, or additional, active ingredients are disclosed in Section 4.3, above.

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

[127] The composition, shape, and type of dosage forms will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms are used will vary from one another will be readily apparent to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 20th ed., Mack Publishing, Easton PA (2000).

[128] In one embodiment, pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, provided are pharmaceutical compositions and dosage forms that contain little, if any, lactose other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

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

[130] Also provided are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the

pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

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

[132] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are, in one embodiment, packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

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

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

[135] In other embodiments, dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the second active agent will depend on the specific agent used, the diseases or disorders being treated

or managed, and the amount(s) of a compound provided herein, and any optional additional active agents concurrently administered to the patient.

4.5.1 ORAL DOSAGE FORMS

[136] Pharmaceutical compositions that are suitable for oral administration can be provided as discrete dosage forms, such as, but not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See generally*, *Remington's Pharmaceutical Sciences*, 20th ed., Mack Publishing, Easton PA (2000).

[137] Oral dosage forms provided herein are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

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

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

[140] Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums

such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

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

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

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

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

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

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

4.5.2 CONTROLLED RELEASE DOSAGE FORMS

[147] Active ingredients such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 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 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. Thus, the compositions provided encompasse single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled release.

[148] 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 subject 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.

[149] 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.

[150] In certain embodiments, the drug 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 (*see*, Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, i.e., thus requiring only a fraction of the systemic dose (*see*, *e.g.*, Goodson, Medical Applications of Controlled Release, vol. 2, pp. 115-138 (1984)). Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)). 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 in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

4.5.3 PARENTERAL DOSAGE FORMS

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

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

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

4.5.4 TOPICAL AND MUCOSAL DOSAGE FORMS

[154] 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 and 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.

[155] 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 and 2000).

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

4.6 KITS

[157] 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.

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

[159] 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.

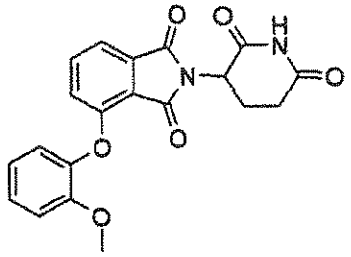
[160] Kits can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration,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

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

Example 1

2-(2,6-Dioxo-piperidin-3-yl)-4-(2-methoxy-phenoxy)-isoindole-1,3-dione



Step 1:

[162] Methyl iodide (30.2 g, 213 mmol) was added to a stirred mixture of 3-nitrophthalic acid (15.0 g, 71.0 mmol) and sodium bicarbonate (23.9 g, 284 mmol) in DMF (150 mL) at room temperature, and the mixture was then heated in an oil bath set to 60 °C for 4 h. The mixture was then poured into 700 mL of ice water. After the ice melted, the mixture was extracted with ethyl acetate (3 x 150 mL) and the organic phases were washed with water (7 x 500 mL), dried ($MgSO_4$) and evaporated, providing 16.2 g of 3-nitrophthalic acid dimethyl ester as a pale yellow solid, in 95% yield; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 4.02 (s, 3H), 7.69 (t, J = 8.1 Hz, 1H), 8.36 (m, 2H).

Step 2:

[163] A mixture of 3:1 ethanol-conc. HCl (200 mL) was cooled to 0 °C and then 3-nitrophthalic acid dimethyl ester (15.0 g, 62.8 mmol) was added. Maintaining the cooling, tin (II) chloride (70.8 g, 314 mmol) was added portionwise, over a period of 15 min. Following completion of the addition, the cooling bath was removed and stirring proceeded at room temperature. After 2 h, the mixture was neutralized by the addition of solid sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate (3 x 150 mL) and the combined extracts were washed with water (5 x 250 mL), were dried ($MgSO_4$) and evaporated, providing 11.3 g of 3-aminophthalic acid dimethyl ester as a yellow oil, in 86% yield; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 3.86 (s, 3H), 5.20 (br, 2H), 6.78 (dd, J = 8.5 Hz, J = 1.0 Hz, 1H), 6.90 (dd, 1H, J = 7.3 Hz, J = 1.0 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H).

Step 3:

[164] A solution of 3-aminophthalic acid dimethyl ester (9.5 g, 45.4 mmol) in 1:1 water-conc. HCl (300 mL) was cooled to 0 °C; during cooling, a precicipitate formed. A solution of $NaNO_2$ (3.5 g, 50.0 mmol) in 10 mL water was then added slowly, maintaining the temperature between 0 – 5 °C throughout the addition. Following completion of the addition, the mixture was stirred at this temperature for 10 minutes before adding a solution of KI (11.3 g, 68.3 mmol) in 30 mL of 1:1 water-conc. HCl. This solution was added all at once, and then the reaction flask was transferred immediately to an oil bath preheated to 65 °C. The mixture stirred with heating for 10 minutes, and was then cooled in an ice bath. The mixture was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic extracts were washed with water (3 x 150 mL), were dried ($MgSO_4$) and evaporated, and the residue was chromatographed using with hexanes-ethyl acetate gradient. The product, which eluted at 17:3 hexanes-ethyl acetate, was a light purple solid, and was then triturated with hexanes, filtered, and dried to give 9.7 g (67%) of 3-iodophthalic acid dimethyl ester, as a colorless

solid; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.99 (s, 3H), 7.19 (t, J = 7.9 Hz, 1H), 8.02 (d, J = 7.9 Hz, 2H).

Step 4:

[165] A mixture of guaiacol (0.77 g, 6.2 mmol), copper (I) bromide (0.89 g, 6.2 mmol), and sodium hydride (0.3 g of a 60% dispersion, 7.5 mmol) in 100 mL pyridine was heated to reflux and stirred under nitrogen for 15 min. 3-Iodophthalic acid dimethyl ester (2.0 g, 6.2 mmol) was added, and the resulting mixture was stirred at reflux for 20 h. The mixture was cooled to room temperature and quenched by the addition of saturated NH_4Cl (15 mL). Volatiles were removed under reduced pressure. The residue was partitioned between dilute aqueous HCl (100 mL) and ethyl acetate (100 mL), and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with dilute aqueous HCl (2 x 100 mL), saturated Na_2CO_3 (2 x 100 mL), again with dilute aqueous HCl (2 x 100 mL) and finally with water (100 mL), and were evaporated. Chromatography in hexanes-ethyl acetate gradient provided 0.75 g of 3-(2-methoxy-phenoxy)-phthalic acid dimethyl ester, eluting at 25-30% ethyl acetate, in 38% yield; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 6.86-6.91 (m, 1H), 6.93-7.01 (m, 2H), 7.05 (dd, J = 7.9 Hz, J = 1.6 Hz, 1H), 7.13-7.20 (m, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.66-7.69 (m, 1H).

Step 5:

[166] A mixture of 3-(2-methoxy-phenoxy)-phthalic acid dimethyl ester (0.75 g, 2.4 mmol) and 3N NaOH (50 mL) in ethanol (100 mL) was heated to reflux for 2 h. The mixture was cooled and the solvent was removed under vacuum. The residue was dissolved in water (100 mL) and washed with CH_2Cl_2 (2 x 100 mL), acidified (HCl), and extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were washed with water (3 x 75 mL), dried ($MgSO_4$), and evaporated, providing 0.53 g of 3-(2-methoxy-phenoxy)-phthalic acid, in 78% yield; ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H), 6.82 (dd, J = 8.4 Hz, J = 0.9 Hz, 1H), 6.95-6.98 (m, 2H), 7.16-7.23 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H).

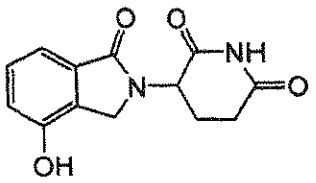
Step 6:

[167] A mixture of 3-(2-methoxy-phenoxy)-phthalic acid (0.51 g, 1.8 mmol) and *rac*-α-aminoglutarimide hydrochloride (0.29 g, 1.8 mmol) in pyridine (10 mL) was heated to reflux for 16 h. The mixture was cooled and evaporated under vacuum. The residue was dissolved in ethyl acetate (100 mL) and washed with dilute aqueous HCl (2 x 100 mL) and water (100 mL), and was evaporated. The residue was chromatographed using a CH_2Cl_2-

methanol gradient, eluting the title compound at 95:5 CH_2Cl_2-methanol, 0.59 g, in 88% yield; mp 223-225 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 µm, 1 mL/min, 240 nm, 40/60 CH_3CN/0.1 % H_3PO_4, 6.06 (99.46%); ^1H NMR (DMSO-d_6) δ 2.06-2.11 (m, 1H), 2.53-2.64 (m, 2H), 2.83-2.90 (m, 1H), 3.75 (s, 1H), 5.15 (dd, J = 12.4 Hz, J = 5.3 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H), 7.21-7.37 (m, 3H), 7.54 (d, J = 7.2 Hz, 1H), 7.72 (t, J = 7.9 Hz, 1H), 11.13 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.9, 31.0, 48.9, 55.7, 113.7, 116.5, 116.7, 120.7, 121.5, 122.3, 127.2, 133.3, 137.0, 141.3, 151.2, 154.7, 165.0, 166.6, 170.0, 172.8; Anal. Calcd for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.24; N, 7.37. Found: C, 63.00; H, 4.24; N, 7.29.

Example 2

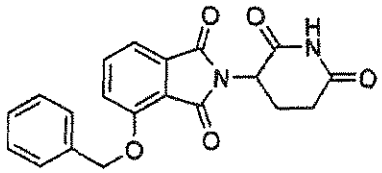
3-(4-hydroxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione



[168] A 250mL-3N-RBF was charged with 3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione and H_2O (10 vol) and cooled to 0-5 °C. $NaNO_2$ (1.1 eq) and HCl (1.1 eq) were added, and the mixture was stirred for 30 minutess. The mixture was then heated to 75-80 °C for 2 hours. The mixture was cooled to room temperature, filtered and dried *in vacuo* (18 h, 35-40 °C). The crude product was purified by prep-HPLC (Conditions: C18 Symmetry Column, 90:10 H_2O: MeCN isocratic, 60 mL/min flow rate, product retention time ~30 min) to give an off-white solid (240 mg, 2.4%, 99.5 HPLC AP); mp 296.39 °C; HPLC: Hypersil DBS C8 5m column, 250 x 4.6 mm, 35 °C; 99:1 to 85:15 Gradient CH_3CN/10 mM aq. KH_2PO_4 , 1.0 mL/min over 20 minutes; 7.60 min, 99.5% AP at 210/240 nm: ^1H-NMR (DMSO-d_6): 10.97 (1H, br s), 10.11 (1H, br s), 7.34 (1H, t), 7.17 (1H, d), 7.03 (1H, d), 5.09 (1H, dd), 4.25 (2H, dd), 2.97-2.85 (1H, m), 2.62-2.36 (2H, m), 2.03-1.96 (1H, m) ppm; ^{13}C-NMR (DMSO-d_6):172.85, 171.04, 168.27, 152.55, 133.41, 129.44, 127.94, 117.97, 113.71, 51.59, 45.09, 31.22, 22.42 ppm; LC-MS ES^+ (M+1) 261; CHN-Analysis, calcd for $C_{13}H_{12}N_2O_4$: C, 60.00%; H, 4.65%; N, 10.76%. Found: C, 59.54%; H, 4.88%; N, 10.48%.

Example 3

4-Benzyloxy-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[169] A mixture of 3-hydroxyphthalic anhydride (4.96 g, 30.2 mmol) in methanol (60 mL) was refluxed for 3 h, cooled to room temperature, and the solvent was evaporated under vacuum. The residue and sodium bicarbonate (7.11 g, 84.6 mmol) were suspended in DMF (40 mL). Iodomethane (4.53 mL, 72.5 mmol) was added and the reaction mixture was heated at 50 °C for 2 h. The solvent was removed under vacuum and the residue was partitioned between ethyl acetate (120 mL) and water (100 mL). The organic phase was washed with water (2 x 100 mL) and evaporated. The residue was chromatographed using a hexanes-ethyl acetate gradient, eluting the product at 6:4 hexanes-ethyl acetate, 4.83 g of 3-hydroxy-phthalic acid dimethyl ester, in 76% yield; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.92 (s, 3H), 6.97 (dd, J = 7.9 Hz, J = 0.9 Hz, 1H), 7.09 (dd, J = 8.6 Hz, J = 1.0 Hz, 1H), 7.46 (t, J = 8.3 Hz, 1H), 10.58 (s, 1H).

Step 2:

[170] Potassium carbonate (1.78 g, 12.9 mmol) and benzyl bromide (0.92 mL, 7.7 mmol) were added to a stirred solution of 3-hydroxy-phthalic acid dimethyl ester (1.35 g, 6.40 mmol) in DMF (15 mL). The reaction mixture was stirred overnight at room temperature and then quenched with cold water (60 mL). The aqueous layer was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed with water (4 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under vacuum. The residue was chromatographed using a hexanes-ethyl acetate gradient, eluting the product at 7:3 hexanes-ethyl acetate, 1.66 g of 3-benzyloxy-phthalic acid dimethyl ester, in 86% yield; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.95 (s, 3H), 5.16 (s, 2H), 7.15 (d, J = 8.4 Hz, 1H), 7.28-7.41 (m, 6H), 7.62 (d, J = 7.9 Hz, 1H).

Step 3:

[171] A mixture of 3-benzyloxy-phthalic acid dimethyl ester (1.64 g, 5.50 mmol) and 3N NaOH (50 mL) in ethanol (100 mL) was heated to reflux for 1 h and cooled to room temperature. The solvent was removed under vacuum and the residue was dissolved in water (100 mL), washed with CH_2Cl_2 (2 x 100 mL) and acidified with 6N HCl to pH 1-2.

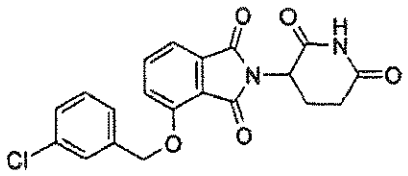
The precipitate was filtered and washed with water (100 mL) to give 3-benzyloxy-phthalic acid as a white solid (1.10 g, 74% yield); ^{1}H NMR (DMSO-d_6) δ 5.20 (s, 2H), 7.29-7.51 (m, 8H), 13.02 (br, 2H).

Step 4:

[172] A mixture of 3-benzyloxy-phthalic acid (1.08 g, 4.00 mmol) and *rac*-α-aminoglutarimide hydrochloride (0.65 g, 4.0 mmol) in pyridine (10 mL) was heated to reflux for 4 h. The reaction mixture was cooled and the solvent was evaporated under vacuum. The residue was suspended in ethyl acetate (200 mL) and washed with dilute aqueous HCl (100 mL). The organic phase was combined with the insoluble precipitate and evaporated to dryness. The resulting solid was triturated with ethyl acetate (100 mL), filtered, washed with additional ethyl acetate (50 mL), and dried to give the title compound (1.66 g, 86% yield); mp 238-240 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 μm, 1 mL/min, 240 nm, 40/60 CH_3CN/0.1 % H_3PO_4, 7.23 (96.71%); ^{1}H NMR (DMSO-d_6) δ 1.99-2.08 (m, 1H), 2.45-2.62 (m, 2H), 2.81-2.94 (m, 1H), 5.10 (dd, J = 12.6 Hz, J = 5.3 Hz, 1H), 5.38 (s, 2H), 7.32-7.53 (m, 6H), 7.60 (d, J = 8.5 Hz, 1H), 7.83 (t, J = 8.2 Hz, 1H), 11.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0, 30.9, 48.8, 70.0, 115.6, 116.6, 120.2, 127.3, 128.0, 128.5, 133.3, 136.2, 137.0, 155.5, 165.3, 166.8, 169.9, 172.8; Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.54; H, 4.35; N, 7.63.

Example 4

4-(3-Chloro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[173] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.3 g, 6.3 mmol) in acetone (20 mL) and potassium carbonate (2.1 g, 15.2 mmol) was added 3-chlorobenzyl bromide (1.0 mL, 7.6 mmol) and refluxed overnight. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL), and washed with water (2 x 100 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(3-chloro-benzyloxy)-phthalic acid dimethyl ester (1.9 g, 92% yield). The product was used in the next step without further purification.

Step 2:

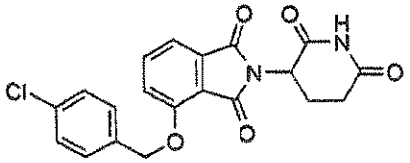
[174] A solution of 3-(3-chloro-benzyloxy)-phthalic acid dimethyl ester (1.9 g, 5.8 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(3-chloro-benzyloxy)-phthalic acid as an off-white solid (1.6 g, 87% yield). The product was used in the next step without further purification.

Step 3:

[175] A mixture of 3-(3-chloro-benzyloxy)-phthalic acid (1.6 g, 5.1 mmol), alpha-amino- glutarimide hydrochloride (0.87 g, 5.3 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(3-chloro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (0.74 g, 37% yield); HPLC: Waters Symmetry C_{18}, 5µm, 3.9 x 150 mm, 1 mL/min, 240 nm, 50/50 CH_3CN/0.1% H_3PO_4, 6.44 min (99.8%); mp, 249-251°C; ^{1}H NMR (DMSO-d_6) δ 2.02-2.07 (m, 1H, CH*H*), 2.54-2.62 (m, 2H, CH_2), 2.83-2.91 (m, 1H, CH*H*), 5.12 (dd, J = 6, 12 Hz, 1H, C*H*), 5.39 (s, 2H, CH_2), 7.40-7.87 (m, 7H, Ar), 11.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.96, 30.92, 48.77, 69.05, 115.72, 116.69, 120.10, 125.65, 126.85, 127.84, 130.42, 133.18, 133.26, 137.07, 138.76, 155.19, 165.32, 166.74, 169.89, 172.75. Anal Calcd For $C_{20}H_{15}N_2O_5Cl$ +0.1 H_2O: C, 59.96; H, 3.82; N, 6.99; Cl, 8.85. Found: C, 59.93; H, 3.54; N, 6.91; Cl, 9.00.

Example 5

4-(4-Chloro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[176] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.3 g, 6.3 mmol) in acetone (20 mL) and potassium carbonate (2.6 g, 19 mmol) was added 4-chlorobenzyl chloride (1.1 g, 6.6 mmol) and refluxed overnight. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL) and

washed with water (2 x 100 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(4-chloro-benzyloxy)-phthalic acid dimethyl ester (2.3 g, 110% crude yield). The product was used in the next step without further purification.

Step 2:

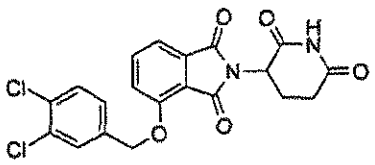
[177] A solution of 3-(4-chloro-benzyloxy)-phthalic acid dimethyl ester (2.2 g, 6.3 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(4-chloro-benzyloxy)-phthalic acid as an off-white solid (1.9 g, 98% yield). The product was used in the next step without further purification.

Step 3:

[178] A mixture of 3-(4-chloro-benzyloxy)-phthalic acid (1.9 g, 6.2 mmol), alpha-amino-glutarimide hydrochloride (1.1 g, 6.5 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(4-chloro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (1.2 g, 49% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 50/50 CH_3CN/0.1% H_3PO_4, 6.64 min (99.9%); mp, 239-241°C; ^{1}H NMR (DMSO-d_6) δ 2.00-2.07 (m, 1H, CH*H*), 2.54-2.62 (m, 2H, CH_2), 2.83-2.95 (m, 1H, CH*H*), 5.12 (dd, J = 6, 12 Hz, 1H, C*H*), 5.38 (s, 2H, CH_2), 7.48-7.86 (m, 7H, Ar), 11.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.96, 30.91, 48.75, 69.18, 115.66, 116.65, 120.16, 128.50, 129.02, 132.52, 133.25, 135.22, 137.03, 155.27, 165.30, 166.74, 169.89, 172.75. Anal Calcd For $C_{20}H_{15}N_2O_5Cl$: C, 60.24; H, 3.79; N, 7.02; Cl, 8.89. Found: C, 60.41; H, 3.63; N, 7.02; Cl, 8.72.

Example 6

4-(3,4-Dichloro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[179] Triethylamine (2.70 mL, 19.4 mmol) was added to a mixture of 3-hydroxyphthalic anhydride (3.00 g, 18.3 mmol) and *rac*-α-aminoglutarimide hydrochloride

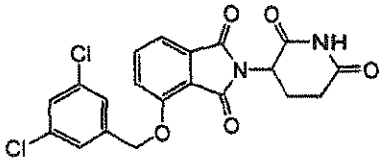
(3.01 g, 18.3 mmol) in DMF (60 mL). The reaction mixture was heated to 90 °C overnight, then cooled to room temperature and the solvent was evaporated under vacuum. The residue was stirred in CH_2Cl_2 (100 mL) for 30 min and the solvent was removed under vacuum. The residue was stirred in water (120 mL) for 2 h and the resulting solid was filtered, washed with water (50 mL) and dried. 1,4-Dioxane (200 mL) was added, and the resulting suspension was stirred for 16 h and filtered; the insoluble material was reserved. The filtrate was treated with decolorizing carbon (2 g) and heated to reflux for 1 h. After cooling to 50 °C, the reaction mixture was filtered through Celite and the filter was washed with additional 1,4-dioxane (50 mL). The filtrate was combined with the insoluble precipitate and evaporated to dryness. The resulting solid was triturated with ethyl acetate (100 mL), filtered and dried to give 2-(2,6-dioxo-piperidin-3-yl)-4-hydroxy-isoindole-1,3-dione, 4.18 g, in 56% yield; ^{1}H NMR (DMSO-d_6) δ 1.99-2.06 (m, 1H), 2.45-2.61 (m, 2H), 2.82-2.96 (m, 1H), 5.08 (dd, J = 12.6 Hz, J = 5.3 Hz, 1H), 7.23-7.33 (m, 2H), 7.66 (dd, J = 8.2 Hz, J = 7.2 Hz, 1H), 11.10 (s, 1H), 11.19 (s, 1H).

Step 2:

[180] A mixture of polymer-supported triphenylphosphine (1.46 g, ~ 4.4 mmol) and 3,4-dichlorobenzyl alcohol (0.65 g, 3.6 mmol) was stirred in THF (10 mL) at 0 °C. Keeping the reaction mixture at 0 °C, a solution of diisopropylazodicarboxylate (0.87 mL, 4.4 mmol) in THF (2.1 mL) was added dropwise. 2-(2,6-Dioxo-piperidin-3-yl)-4-hydroxy-isoindole-1,3-dione (1.00 g, 3.60 mmol) was then added as a solid, the reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The solvent was evaporated under vacuum and the residue was chromatographed using a methanol-CH_2Cl_2 gradient, eluting the product at 95:5 CH_2Cl_2-methanol. This material was dissolved in ethyl acetate (150 mL) and water (100 mL) was added. The organic phase was then washed with 10% dilute aqueous sodium carbonate (2 x 50 mL) and water (3 x 50 mL). The solvent was removed under vacuum and the resulting solid was triturated with ether, filtered and dried to provide the title compound as a white solid (0.41 g, 26% yield); mp 245-247 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 μm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1 % H_3PO_4, 3.50 (99.78%); ^{1}H NMR (DMSO-d_6) δ 2.02-2.07 (m, 1H), 2.45-2.62 (m, 2H), 2.82-2.96 (m, 1H), 5.12 (dd, J = 12.6 Hz, J = 5.4 Hz, 1H), 5.38 (s, 2H), 7.49-7.51 (m, 2H), 7.57 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.81-7.88 (m, 2H), 11.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0, 30.9, 48.8, 68.5, 115.9, 116.8, 120.1, 127.3, 129.0, 130.5, 130.8, 131.2, 133.3, 137.1, 137.5, 155.1, 165.3, 166.8, 169.9, 172.8; Anal. Calcd for $C_{20}H_{14}N_2O_5Cl_2$ + 0.3 H_2O: C, 54.76; H, 3.35; N, 6.39. Found: C, 54.48; H, 3.07; N, 6.29.

Example 7

4-(3,5-Dichloro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[181] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (0.5 g, 2.4 mmol), (3,5-dichloro-phenyl)-methanol (0.84 g, 4.8 mmol), and polymer-supported triphenyl phosphine (1.5 g, 4.8 mmol) in THF (30 mL) in ice-bath was slowly added diisopropyl azodicarboxylate (1.0 mL, 4.8 mmol) and stirred at r.t. overnight. The mixture was filtered and the solid was washed with ethyl acetate (10 mL). The filtrate was evaporated and the residue was purified by flash column chromatography (EtOAc/Hexane) to give 3-(3,5-dichloro-benzyloxy)-phthalic acid dimethyl ester (0.42 g, 48% yield). The *product was used in the next step without further purification.*

Step 2:

[182] A solution of 3-(3,5-dichloro-benzyloxy)-phthalic acid dimethyl ester (0.42 g, 1.2 mmol) in reagent alcohol (10 mL) and 3 N sodium hydroxide (10 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (10 mL) and washed with methylene chloride (2 x 10 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers was washed with water (2 x 10 mL), dried and concentrated to give 3-(3,5-dichloro-benzyloxy)-phthalic acid as an off-white solid (0.34 g, 88% yield). The product was used in the next step without further purification.

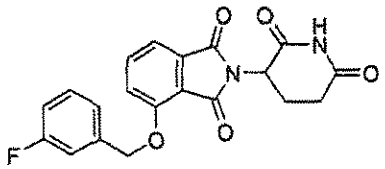
Step 3:

[183] A mixture of 3-(3,5-dichloro-benzyloxy)-phthalic acid (0.3 g, 0.9 mmol), alpha-amino-glutarimide hydrochloride (0.15 g, 0.92 mmol) in pyridine (10 mL) was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(3,5-dichloro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (0.30 g, 84% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 70/30 CH_3CN/0.1% H_3PO_4, 3.6 min (98.0%); mp, 278-280°C; ^{1}HNMR (DMSO-d_6) δ 2.01-2.08 (m, 1H, CH*H*), 2.54-2.63 (*m*, 2H, C*H*$_2$), 2.84-2.96 (m, 1H, C*HH*), 5.13 (dd, *J* = 6, 12 Hz, 1H, *CH*), 5.40 (s, 2H, C*H*$_2$), 7.50-7.89 (m, 6H, Ar), 11.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.95, 30.92, 48.79, 68.37, 115.90, 116.79, 120.02, 125.58, 127.45, 133.25, 134.18, 137.14, 140.61,

154.93, 165.34, 166.73, 169.88, 172.73. Anal Calcd For $C_{20}H_{14}N_2O_5Cl_2$: C, 55.45; H, 3.26; N, 6.47; Cl, 16.37. Found: C, 55.20; H, 3.13; N, 6.38; Cl, 16.63.

Example 8

4-(3-Fluoro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[184] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.4 g, 6.7 mmol) in acetone (30 mL) and potassium carbonate (2.8 g, 20 mmol) was added 3-fluorobenzyl bromide (0.89 mL, 7.0 mmol) and refluxed overnight. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL) and washed with water (2 x 100 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(3-fluoro-benzyloxy)-phthalic acid dimethyl ester (2.4 g, 113% crude yield). The product was used in the next step without further purification.

Step 2:

[185] A solution of 3-(3-fluoro-benzyloxy)-phthalic acid dimethyl ester (2.4 g crude, 6.7 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(3-fluoro-benzyloxy)-phthalic acid as an off-white solid (1.9 g, 101% crude yield). The product was used in the next step without further purification.

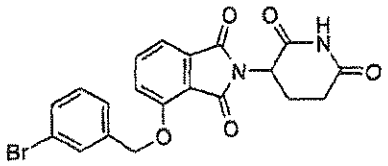
Step 3:

[186] A mixture of 3-(3-fluoro-benzyloxy)-phthalic acid (1.9 g, 6.7 mmol), alpha-amino-glutarimide hydrochloride (1.2 g, 7.0 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(3-fluoro-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (2.3 g, 89% yield); HPLC: Waters Symmetry C_{18}, 5µm, 3.9 x 150 mm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1% H_3PO_4, 2.22 min (99.9%); mp, 241-243°C; ^{1}H NMR (DMSO-d_6) δ 2.01-2.08 (m, 1H, CH*H*), 2.55-2.62 (m, 2H, CH_2), 2.83-2.95 (m, 1H, CH*H*), 5.11 (dd, J = 6, 12 Hz, 1H, *CH*), 5.40 (s, 2H, CH_2), 7.15-7.87 (m, 7H, Ar),

11.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.96, 30.92, 48.77, 69.11, 113.61, 113.90, 114.52, 114.80, 115.71, 116.70, 120.13, 122.96, 122.99, 130.49, 130.60, 133.25, 137.05, 139.08, 139.18, 155.21, 160.59, 163.81, 165.33, 166.74, 169.89, 172.73. Anal Calcd For $C_{20}H_{15}N_2O_5F$: C, 62.83; H, 3.95; N, 7.33; F 4.97. Found: C, 62.72; H, 3.75; N, 7.27; F, 5.02.

Example 9

4-(3-Bromo-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[187] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.3 g, 6.2 mmol) in acetone (30 mL) and potassium carbonate (2.5 g, 18.4 mmol) was added 3-bromobenzyl bromide (1.6 g, 6.4 mmol) and refluxed overnight. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL) and washed with water (2 x 100 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(3-bromo-benzyloxy)-phthalic acid dimethyl ester (2.5 g, 109% crude yield). The product was used in the next step without further purification.

Step 2:

[188] A solution of 3-(3-bromo-benzyloxy)-phthalic acid dimethyl ester (1.9 g, 5.8 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined extracts was washed with water (2 x 100 mL), dried and concentrated to give 3-(3-bromo-benzyloxy)-phthalic acid as an off-white solid (2.5 g, 109% crude yield). The product was used in the next step without further purification.

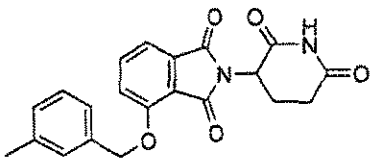
Step 3:

[189] A mixture of 3-(3-bromo-benzyloxy)-phthalic acid (2.4 g, 6.7 mmol), alpha-amino-glutarimide hydrochloride (1.2 g, 7.1 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(3-bromo-benzyloxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (1.8 g, 62% yield); HPLC: Waters Symmetry C_{18}, 5μm,

3.9 x 150 mm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1% H_3PO_4, 3.55 min (99.9%); mp, 246-248°C; ^{1}H NMR (DMSO-d_6) δ 2.03-2.08 (m, 1H, CH*H*), 2.54-2.62 (m, 2H, CH_2), 2.83-2.95 (m, 1H, CH*H*), 5.12 (dd, J = 6, 12 Hz, 1H, C*H*), 5.39 (s, 2H, CH_2), 7.37-7.88 (m, 7H, Ar), 11.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.96, 30.92, 48.77, 69.00, 115.72, 116.69, 120.10, 121.76, 126.05, 129.75, 130.69, 130.74, 133.26, 137.07, 138.99, 155.19, 165.31, 166.74, 169.89, 172.74. Anal Calcd For $C_{20}H_{15}N_2O_5Br$: C, 54.19; H, 3.41; N, 6.32; Br 18.03. Found: C, 54.02; H, 3.22; N, 6.27; Br, 17.81.

Example 10

2-(2,6-Dioxo-piperidin-3-yl)-4-(3-methyl-benzyloxy)-isoindole-1,3-dione



Step 1:

[190] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.4 g, 6.4 mmol) in acetone (30 mL) and potassium carbonate (2.7 g, 19.3 mmol) was added 1-bromomethyl-3-methyl-benzene (0.91 mL, 6.7 mmol) and refluxed overnight. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL) and washed with water (2 x 100 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(3-methyl-benzyloxy)-phthalic acid dimethyl ester (2.3 g, 115% crude yield). The product was used in the next step without further purification.

Step 2:

[191] A solution of 3-(3-methyl-benzyloxy)-phthalic acid dimethyl ester (2.0 g crude, 6.4 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(3-methyl-benzyloxy)-phthalic acid as an off-white solid (3.0 g, 130% crude yield). The product was used in the next step without further purification.

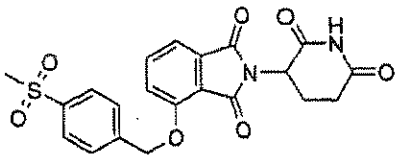
Step 3:

[192] A mixture of 3-(3-methyl-benzyloxy)-phthalic acid (1.8 g, 6.4 mmol), alpha-amino-glutarimide hydrochloride (1.1 g, 6.8 mmol) in pyridine was refluxed overnight. The

mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 2-(2,6-dioxo-piperidin-3-yl)-4-(3-methyl-benzyloxy)-isoindole-1,3-dione as a white solid (1.2 g, 48% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1% H_3PO_4, 3.16 min (99.9%); mp, 195-197°C; ^{1}H NMR (DMSO-d_6) δ 2.00-2.07 (m, 1H, CH*H*), 2.33 (s, 3H, C*H*$_3$), 2.54-2.62 (m, 2H, C*H*$_2$), 2.83-2.95 (m, 1H, CH*H*), 5.10 (dd, J = 6, 12 Hz, 1H, C*H*), 5.33 (s, 2H, C*H*$_2$), 7.15-7.85 (m, 7H, Ar), 11.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.00, 21.96, 30.92, 48.74, 70.08, 115.49, 116.58, 120.19, 124.40, 127.85, 128.40, 128.60, 133.26, 136.03, 136.98, 137.64, 155.53, 165.30, 166.77, 169.91, 172.75. Anal Calcd For $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.50; H, 4.79; N, 7.34.

Example 11

2-(2,6-Dioxo-piperidin-3-yl)-4-(4-methanesulfonyl-benzyloxy)-isoindole-1,3-dione



Step 1:

[193] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.3 g, 6.1 mmol) in acetone (25 mL) and potassium carbonate (2.5 g, 18 mmol) was added 1-bromomethyl-4-methanesulfonyl-benzene (1.6 g, 6.4 mmol) and refluxed overnight. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL) and washed with water (2 x 100 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(4-methanesulfonyl-benzyloxy)-phthalic acid dimethyl ester (2.4 g, 104% crude yield). The product was used in the next step without further purification.

Step 2:

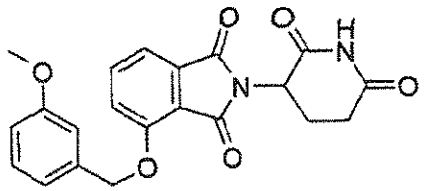
[194] A solution of 3-(4-methanesulfonyl-benzyloxy)-phthalic acid dimethyl ester (2.3 g, 6.1 mmol) in reagent alcohol (140 mL) and 3 N sodium hydroxide (70 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(4-methanesulfonyl-benzyloxy)-phthalic acid as an off-white solid (2.15 g, 101% crude yield). The product was used in the next step without further purification.

Step 3:

[195] A mixture of 3-(4-methanesulfonyl-benzyloxy)-phthalic (2.1 g, 6.1 mmol), alpha-amino-glutarimide hydrochloride (1.1 g, 6.4 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 2-(2,6-dioxo-piperidin-3-yl)-4-(4-methanesulfonyl-benzyloxy)-isoindole-1,3-dione as a white solid (1.3 g, 47% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 35/65 CH_3CN/0.1% H_3PO_4, 2.09 min (99.9%); mp, 293-295°C; ^{1}H NMR (DMSO-d_6) δ 2.03-2.07 (m, 1H, CH*H*), 2.54-2.63 (m, 2H, CH_2), 2.85-2.90 (m, 1H, CH*H*), 3.23 (s, 3H, CH_3SO_2), 5.11 (dd, J = 6, 12 Hz, 1H, C*H*), 5.52 (s, 2H, CH_2), 7.49-8.00 (m, 7H, Ar), 11.13 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.97, 30.91, 43.46, 48.78, 69.09, 115.82, 116.73, 120.11, 127.21, 127.62, 133.28, 137.10, 140.26, 142.17, 155.12, 165.30, 166.73, 169.89, 172.75. Anal Calcd For $C_{21}H_{18}N_2O_7S$ + 0.2 H_2O: C, 56.55; H, 4.16; N, 6.28; S, 7.19. Found: C, 56.32; H, 3.80; N, 6.16; S, 7.20.

Example 12

2-(2,6-Dioxo-piperidin-3-yl)-4-(3-methoxy-benzyloxy)-isoindole-1,3-dione



Step 1:

[196] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.1 g, 5.2 mmol) in acetone (45 mL) and potassium carbonate (2.2 g, 15.7 mmol) was added 1-bromomethyl-3-methoxy-benzene (0.77 mL, 5.5 mmol) and refluxed for three hours. The solvent was evaporated and the residue was partitioned between water (50 mL) and ethyl acetate (80 mL) and washed with water (2 x 50 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(3-methoxy-benzyloxy)-phthalic acid dimethyl ester (2.1 g, 118% crude yield). The product was used in the next step without further purification.

Step 2:

[197] A solution of 3-(3-methoxy-benzyloxy)-phthalic acid dimethyl ester (2.0 g crude, 5.5 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (35 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water

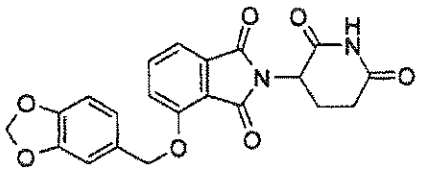
(80 mL) and washed with methylene chloride (3 x 70 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 60 mL) and the combined organic layers was washed with water (2 x 70 mL), dried and concentrated to give 3-(3-methoxy-benzyloxy)-phthalic acid as an off-white solid (1.6 g, 98% crude yield). The product was used in the next step without further purification.

Step 3:

[198] A mixture of 3-(3-methoxy-benzyloxy)-phthalic acid (1.5 g, 5.2 mmol), alpha-amino-glutarimide hydrochloride (0.89 g, 5.4 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 2-(2,6-dioxo-piperidin-3-yl)-4-(3-methoxy-benzyloxy)-isoindole-1,3-dione as a white solid (0.25 g, 12% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1% H_3PO_4, 2.41 min (99.1%); mp, 197-201°C; ^{1}H NMR (DMSO-d_6) δ 2.02-2.06 (m, 1H, CH*H*), 2.59-2.62 (m, 2H, CH_2), 2.83-2.90 (m, 1H, CH*H*), 3.77 (s, 3H, CH_3), 5.10 (dd, J = 6, 12 Hz, 1H, C*H*), 5.35 (s, 2H, CH_2), 6.89-7.85 (m, 7H, Ar), 11.11 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.95, 30.92, 48.75, 55.01, 69.80, 112.72, 113.27, 115.55, 116.66, 119.17, 120.21, 129.61, 133.25, 136.98, 137.74, 155.42, 159.35, 165.32, 166.77, 169.90, 172.74. Anal Calcd For $C_{21}H_{18}N_2O_6$ + 0.1 H_2O: C, 63.67; H, 4.63; N, 7.07. Found: C, 63.49; H, 4.40; N, 7.00.

Example 13

4-(Benzo[1,3]dioxol-5-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[199] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.0 g, 4.8 mmol), benzo[1,3]dioxol-5-yl-methanol (1.4 g, 9.5 mmol), and polymer-supported triphenyl phosphine (3.0 g, 9.5 mmol) in THF (30 mL) in an ice-bath was slowly added diisopropyl azodicarboxylate (1.9 mL, 9.5 mmol) and stirred at r.t. overnight. The mixture was filtered and the filter was washed with ethyl acetate (10 mL). The filtrate was evaporated and the residue was purified by flash column chromatography (EtOAc/Hexane) to give 3-(benzo[1,3]dioxol-5-ylmethoxy)-phthalic acid dimethyl ester (1.7 g, 102% crude yield). The product was used in the next step without further purification.

Step 2:

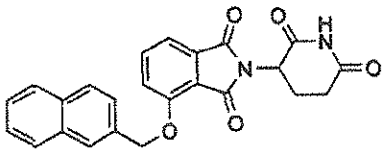
[200] A solution of 3-(benzo[1,3]dioxol-5-ylmethoxy)-phthalic acid dimethyl ester (1.6 g crude, 4.8 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (35 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (80 mL) and washed with methylene chloride (3 x 70 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 60 mL) and the combined organic layers was washed with water (2 x 70 mL), dried and concentrated to give 3-(benzo[1,3]dioxol-5-ylmethoxy)-phthalic acid as an off-white solid (1.2 g, 80% crude yield). The product was used in the next step without further purification.

Step 3:

[201] A mixture of 3-(benzo[1,3]dioxol-5-ylmethoxy)-phthalic acid (1.2 g, 3.8 mmol), alpha-amino-glutarimide hydrochloride (0.66 g, 4.0 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(benzo[1,3]dioxol-5-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (0.45 g, 29% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 50/50 CH_3CN/0.1% H_3PO_4, 4.06 min (98.6%); mp, 229-231°C; ^{1}H NMR (DMSO-d_6) δ 2.02-2.05 (m, 1H, CH*H*), 2.55-2.62 (m, 2H, CH_2), 2.82-2.94 (m, 1H, C*H*H), 5.10 (dd, J = 6, 12 Hz, 1H, C*H*), 5.26 (s, 2H, CH_2), 6.03 (s, 2H, CH_2), 6.93-7.85 (m, 6H, Ar), 11.11 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.95, 30.91, 48.74, 70.00, 101.05, 108.10, 108.18, 115.49, 116.61, 120.28, 121.25, 129.78, 133.24, 136.95, 147.04, 147.38, 155.44, 165.30, 166.76, 169.89, 172.74. Anal Calcd For $C_{21}H_{16}N_2O_7$: C, 61.77; H, 3.95; N, 6.86. Found: C, 61.44; H, 3.72; N, 6.79.

Example 14

2-(2,6-Dioxo-piperidin-3-yl)-4-(naphthalene-2-ylmethoxy)-isoindole-1,3-dione

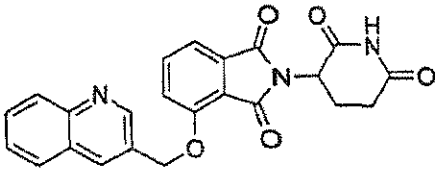


[202] A mixture of triphenylphosphine (1.15 g, 4.40 mmol) and 2-naphthalenemethanol (0.58 g, 3.6 mmol) was stirred in THF (10 mL) at 0 °C. Keeping the reaction mixture at 0 °C, a solution of diisopropylazodicarboxylate (0.87 mL, 4.4 mmol) in THF (2.1 mL) was added dropwise. 2-(2,6-Dioxo-piperidin-3-yl)-4-hydroxy-isoindole-1,3-dione (1.00 g, 3.60 mmol) was then added as a solid, the reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The precipitate was filtered, washed with additional THF (10 mL) and dried. The resulting solid was stirred in hexane (50 mL) for 2

h, filtered and dried. The resulting solid was heated to reflux in methanol (50 mL) for 1 h, filtered and dried to afford the product as a white solid (0.46 g, 30% yield); mp > 260 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 µm, 1 mL/min, 240 nm, 50/50 CH_3CN/0.1 % H_3PO_4, 6.20 (99.48%); ^{1}H NMR (DMSO-d_6) δ 2.02-2.07 (m, 1H), 2.44-2.62 (m, 2H), 2.82-2.97 (m, 1H), 5.12 (dd, J = 12.5 Hz, J = 5.3 Hz, 1H), 5.54 (s, 2H), 7.46-8.05 (m, 10H), 11.13 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0, 31.0, 48.8, 70.3, 115.6, 116.7, 120.4, 125.3, 126.1, 126.3, 126.4, 127.7, 127.8, 128.2, 132.6, 132.7, 133.3, 133.8, 137.0, 155.6, 165.4, 166.8, 169.9, 172.8; Anal. Calcd for $C_{24}H_{18}N_2O_5$: C, 69.39; H, 4.02; N, 6.61. Found: C, 69.56; H, 4.38; N, 6.76.

Example 15

2-(2,6-Dioxo-piperidin-3-yl)-4-(quinolin-3-ylmethoxy)-isoindole-1,3-dione



Step 1:

[203] 3-Quinolinecarbaldehyde (2.00 g, 12.7 mmol) was dissolved in 25 mL of methanol. To this solution was added sodium borohydride (0.24 g, 6.4 mmol) in small portions over a period of 20 minutes. Then 2 mL of water were added and the mixture was evaporated. The residue was dissolved in ethyl acetate (75 mL) and washed with water (3 x 75 mL), dried ($MgSO_4$) and evaporated, providing 1.8 g of quinolin-3-yl-methanol in 90% yield; ^{1}H NMR (DMSO-d_6) δ 4.89 (s, 2H), 7.53 (t, J = 7.1 Hz, 1H), 7.64-7.71 (m, 1H), 7.77 (d, J = 8.2 Hz, 1H), 8.04-8.12 (m, 2H), 8.83 (d, J = 2.0 Hz, 1H).

Step 2:

[204] A mixture of polymer-supported PPh_3 (3.1 g, ~ 9.5 mmol) and quinolin-3-yl-methanol (0.76 g, 4.8 mmol) in 20 mL THF was cooled to 0 °C under N_2. Diisopropyl azodicarboxylate (1.9 g, 9.5 mmol) was added dropwise, and subsequently 3-hydroxy-phthalic acid dimethyl ester (1.0 g, 4.8 mmol) was added as a solid. The mixture stirred for an additional hour at 0 °C and was then allowed to warm to room temperature. After stirring for 16 h, the mixture was filtered. The filter was washed with ethyl acetate (25 mL) and the combined filtrates were evaporated.

Step 3:

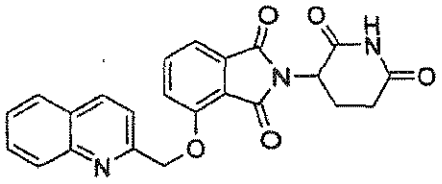
[205] The crude product from Step 2 was dissolved in a mixture of 3N NaOH (50 mL) and ethanol (100 mL), and the resulting solution was heated to reflux for 2 h. The mixture was cooled and the solvent was removed under vacuum. The residue was dissolved in water (100 mL) and washed with CH_2Cl_2 (3 x 100 mL), acidified to pH 2-3 (HCl). The resulting precipitate was filtered and washed with additional water and then ethyl acetate, and dried under vacuum.

Step 4:

[206] The crude product from Step 3 and *rac*-α-aminoglutarimide hydrochloride (0.78 g, 4.8 mmol) in pyridine (10 mL) was heated to reflux for 16 h. The mixture was cooled and evaporated under vacuum. The residue was chromatographed using a CH_2Cl_2-methanol gradient, eluting the title compound at 95:5 CH_2Cl_2-methanol, 0.37 g, in 20% yield over 3 steps; mp 263-265 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 µm, 1 mL/min, 240 nm, 40/60 CH_3CN/water, 3.75 (97.84%); ^1H NMR (DMSO-d_6) δ 2.02-2.06 (m, 1H), 2.55-2.62 (m, 2H), 2.81-2.90 (m, 1H), 5.11 (dd, J = 12.3 Hz, J = 5.3 Hz, 1H), 5.61 (s, 2H), 7.51 (d, J = 7.2 Hz, 1H), 7.62-7.71 (m, 2H), 7.77-7.90 (m, 2H), 8.00-8.08 (m, 2H), 8.48 (s, 1H), 9.04 (d, J = 1.8 Hz, 1H), 11.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0, 30.9, 48.8, 68.3, 115.9, 116.8, 120.4, 127.1, 127.2, 128.1, 128.8, 129.3, 129.8, 133.3, 134.5, 137.1, 147.3, 150.3, 155.3, 165.3, 166.8, 169.9, 172.8; Anal. Calcd for $C_{23}H_{17}N_3O_5 \cdot 0.4$ H_2O: C, 65.37; H, 4.25; N, 9.94. Found: C, 65.35; H, 4.06; N, 9.92.

Example 16

2-(2,6-Dioxo-piperidin-3-yl)-4-(quinolin-2-ylmethoxy)-isoindole-1,3-dione



Step 1:

[207] 2-Quinolinecarbaldehyde (2.00 g, 12.7 mmol) was dissolved in 25 mL of methanol. To this solution was added sodium borohydride (0.24 g, 6.4 mmol) in small portions over a period of 20 minutes. Then 2 mL of water were added and the mixture was evaporated. The residue was dissolved in ethyl acetate (75 mL) and washed with water (3 x 75 mL) and evaporated. The residue was chromatographed in CH_2Cl_2-methanol gradient, eluting the product at 97:3 CH_2Cl_2-methanol, and providing 1.7 g of quinolin-2-yl-methanol in 85% yield; ^1H NMR ($CDCl_3$) δ 4.92 (s, 2H), 7.26 (d, J = 2.1 Hz, 1H), 7.30-7.57 (m, 1H),

7.68-7.75 (m, 1H), 7.82 (dd, J = 8.0 Hz, J = 0.9 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H).

Step 2:

[208] A mixture of polymer-supported PPh_3 (3.1 g, ~ 9.5 mmol) and quinolin-2-yl-methanol (0.76 g, 4.8 mmol) in 20 mL THF was cooled to 0 °C under N_2. Diisopropylazodicarboxylate (1.9 g, 9.5 mmol) was added dropwise, and subsequently 3-hydroxy-phthalic acid dimethyl ester (1.0 g, 4.8 mmol) was added as a solid. The mixture stirred for an additional hour at 0 °C and was then allowed to warm to room temperature. After stirring for 16 h, the mixture was filtered. The filter was washed with ethyl acetate (25 mL) and the combined filtrates were evaporated.

Step 3:

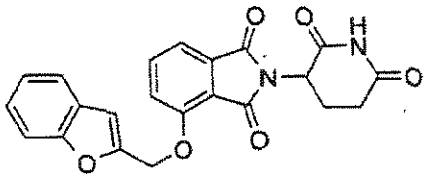
[209] The crude product from Step 2 was dissolved in a mixture of 3N NaOH (50 mL) and ethanol (100 mL), and the resulting solution was heated to reflux for 2 h. The mixture was cooled and the solvent was removed under vacuum. The residue was dissolved in water (100 mL) and washed with CH_2Cl_2 (3 x 100 mL), acidified to pH 2-3 (HCl). The resulting precipitate was filtered and washed with additional water and then ethyl acetate, and dried under vacuum.

Step 4:

[210] The product from Step 3 and *rac*-α-aminoglutarimide hydrochloride (0.78 g, 4.8 mmol) in pyridine (10 mL) was heated to reflux for 16 h. The mixture was cooled and evaporated under vacuum. The residue was chromatographed using a CH_2Cl_2-methanol gradient, eluting the product at 95:5 CH_2Cl_2-methanol. This material was triturated in DMF (5 mL), filtered and washed with additional 2 mL of DMF, and dried under vacuum. This material was then purified by preparative HPLC using a mobile phase of 35/65 acetonitrile-water, providing 75 mg of the title compound in 4% yield over 3 steps; mp 254-256 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 μm, 1 mL/min, 240 nm, 30/70 CH_3CN/0.1% H_3PO_4, 7.02 (94.00%); ^{1}H NMR (DMSO-d_6) δ 2.03-2.08 (m, 1H), 2.57-2.64 (m, 2H), 2.85-2.96 (m, 1H), 5.13 (dd, J = 12.2 Hz, J = 4.9 Hz, 1H), 5.62 (s, 2H), 7.50 (d, J = 7.1 Hz, 1H), 7.62-7.66 (m, 2H), 7.77-7.87 (m, 3H), 8.00-8.03 (m, 2H), 8.48 (d, J = 8.5 Hz, 1H), 11.13 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0, 31.0, 48.8, 71.4, 115.8, 116.8, 119.1, 120.3, 126.7, 127.2, 128.0, 128.5, 130.0, 133.3, 137.1, 137.2, 146.9, 155.3, 156.7, 165.4, 166.8, 169.9, 172.8; Anal. Calcd for $C_{23}H_{17}N_3O_5 \cdot 1.6\ H_2O$: C, 62.19; H, 4.58; N, 9.46. Found: C, 62.20; H, 3.97; N, 9.15.

Example 17

4-(Benzofuran-2-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[211] 2-Benzofurancarbaldehyde (2.2 g, 15 mmol) was dissolved in 25 mL of methanol. To this solution was added sodium borohydride (0.28 g, 7.5 mmol) in small portions over a period of 20 minutes. Then 2 mL of water were added and the mixture was evaporated. The residue was dissolved in ethyl acetate (75 mL) and washed with water (3 x 75 mL), dried ($MgSO_4$) and evaporated, providing 2.1 g of benzofuran-2-yl-methanol, in 95% yield; ^{1}H NMR ($CDCl_3$) δ 2.03 (t, J = 6.1 Hz, 1H), 4.77 (d, J = 6.1 Hz, 2H), 6.66 (s, 1H), 7.19-7.32 (m, 2H), 7.45-7.50 (m, 1H), 7.53-7.57 (m, 1H).

Step 2:

[212] A mixture of polymer-supported PPh_3 (3.1 g, ~ 9.5 mmol) and benzofuran-2-yl-methanol (0.70 g, 4.8 mmol) in 20 mL THF was cooled to 0 °C under N_2. Diisopropylazodicarboxylate (1.9 g, 9.5 mmol) was added dropwise, and subsequently 3-

hydroxy-phthalic acid dimethyl ester (1.0 g, 4.8 mmol) was added as a solid. The mixture stirred for an additional hour at 0 °C and was then allowed to warm to room temperature. After stirring for 16 h, the mixture was filtered. The filter was washed with ethyl acetate (25 mL) and the combined filtrates were evaporated. The residue was dissolved in 75 mL ethyl acetate and washed with Na_2CO_3 (2 x 75 mL) and water (2 x 75 mL), dried ($MgSO_4$), and evaporated.

Step 3:

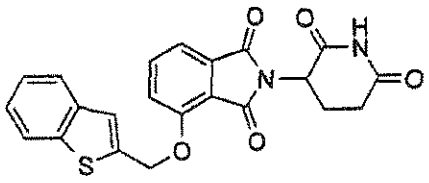
[213] The crude product from Step 2 was dissolved in a mixture of 3N NaOH (50 mL) and ethanol (100 mL), and the resulting solution was heated to reflux for 2 h. The mixture was cooled and the solvent was removed under vacuum. The residue was dissolved in water (100 mL) and washed with CH_2Cl_2 (3 x 100 mL), acidified (HCl), and extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were washed with water (3 x 75 mL), dried ($MgSO_4$) and evaporated, providing 0.86 g of 3-(benzofuran-2-ylmethoxy)-phthalic acid, in 57% yield over two steps; ^{1}H NMR (DMSO-d_6) δ 5.35 (s, 2H), 7.04 (s, 1H), 7.22-7.37 (m, 2H), 7.45-7.67 (m, 5H).

Step 4:

[214] A mixture of 3-(benzofuran-2-ylmethoxy)-phthalic acid (0.55 g, 1.8 mmol) and *rac*-α-aminoglutarimide hydrochloride (0.30g, 1.8 mmol) in pyridine (10 mL) was heated to reflux for 16 h. The mixture was cooled and evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with dilute aqueous HCl (2 x 100 mL) and water (2 x 100 mL) and was evaporated. The residue was chromatographed using a CH_2Cl_2-methanol gradient, eluting the title compound at 95:5 CH_2Cl_2-methanol, 0.46 g, in 65% yield; mp 234-236 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 μm, 1 mL/min, 240 nm, 50/50 CH_3CN/0.1% H_3PO_4, 4.16 (98.58%); ^{1}H NMR (DMSO-d_6) δ 1.99-2.04 (m, 1H), 2.43-2.61 (m, 2H), 2.81-2.95 (m, 1H), 5.08 (dd, J = 12.7 Hz, J = 5.3 Hz, 1H), 5.55 (s, 2H), 7.14 (s, 1H), 7.23-7.37 (m, 2H), 7.50 (d, J = 7.0 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.86 (t, J = 7.8 Hz, 1H), 11.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.9, 30.9, 48.8, 63.1, 107.4, 111.3, 115.9, 116.7, 120.2, 121.6, 123.1, 125.0, 127.5, 133.3, 137.0, 152.0, 154.6, 155.0, 165.2, 166.7, 169.9, 172.7; Anal. Calcd for $C_{22}H_{16}N_2O_6 \cdot 0.15\ H_2O$: C, 64.91; H, 4.04; N, 6.88. Found: C, 64.89; H, 3.99; N, 6.84.

Example 18

4-(Benzo[b]thiophen-2-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[215] A mixture of polymer-supported PPh_3 (3.1 g, ~ 9.5 mmol) and 1-benzothiophen-2-yl-methanol (1.0 g, 6.1 mmol) in 20 mL THF was cooled to 0 °C under N_2. Diisopropylazodicarboxylate (1.9 g, 9.5 mmol) was added dropwise, and subsequently 3-hydroxy-phthalic acid dimethyl ester (1.0 g, 4.8 mmol) was added as a solid. The mixture stirred for an additional hour at 0 °C and was then allowed to warm to room temperature. After stirring for 16 h, the mixture was filtered. The filter was washed with ethyl acetate (25 mL) and the combined filtrates were evaporated.

Step 2:

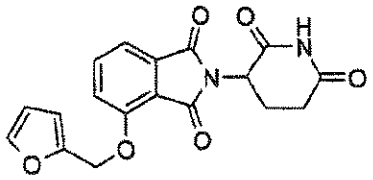
[216] The crude product from Step 1 was dissolved in a mixture of 3N NaOH (50 mL) and ethanol (100 mL), and the resulting solution was heated to reflux for 2 h. The mixture was cooled and the solvent was removed under vacuum. The residue was dissolved in water (100 mL) and washed with CH_2Cl_2 (3 x 100 mL), acidified (HCl), and extracted into ethyl acetate (3 x 75 mL). The combined organic extracts were washed with water (3 x 75 mL), dried ($MgSO_4$), and evaporated.

Step 3:

[217] The crude product from Step 2 and *rac*-α-aminoglutarimide hydrochloride (0.40 g, 2.5 mmol) in pyridine (10 mL) was heated to reflux for 16 h. The mixture was cooled and evaporated under vacuum. The residue was chromatographed using a CH_2Cl_2-methanol gradient, eluting the product at 95:5 CH_2Cl_2-methanol, and providing 0.40 g in 30% yield over 3 steps; mp 247-249 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 µm, 1 mL/min, 240 nm, 50/50 CH_3CN/0.1% H_3PO_4, 5.68 (100.00%); ^1H NMR (DMSO-d_6) δ 2.01-2.06 (m, 1H), 2.44-2.61 (m, 2H), 2.82-2.96 (m, 1H), 5.10 (dd, J = 12.6 Hz, J = 5.3 Hz, 1H), 5.71 (s, 2H), 7.32-7.42 (m, 2H), 7.49 (d, J = 7.1 Hz, 1H), 7.58 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.80-7.87 (m, 2H), 7.96 (d, J = 8.2 Hz, 1H), 11.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0, 30.9, 48.8, 66.1, 115.9, 116.9, 120.4, 122.6, 123.8, 123.9, 124.5, 124.7, 133.3, 136.9, 138.9, 139.5, 154.9, 165.2, 166.7, 169.9, 172.8; Anal. Calcd for $C_{22}H_{16}N_2O_5S$: C, 62.85; H, 3.84; N, 6.66. Found: C, 62.88; H, 3.46; N, 6.57.

Example 19

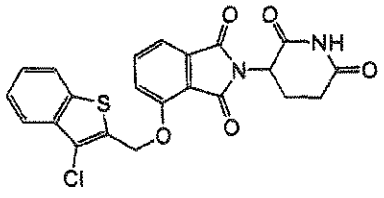
2-(2,6-Dioxo-piperidin-3-yl)-4-(furan-2-ylmethoxy)-isoindole-1,3-dione



[218] To a solution of triphenylphosphine (630 mg, 2.4 mmol) and furan-2-yl-methanol (0.17 mL, 2.0 mmol) in THF (10 mL) was added a solution of DEAD (0.38 mL, 2.4 mmol) in THF (0.6 mL) at 0 °C. After 5 min, 4-hydroxy-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (550 mg, 2.0 mmol) was added to the mixture. The mixture was allowed to warm to room temperature and kept for 4h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (Silca Gel) to give an oil. The oil was slurried in methanol (10 mL) for 3h to give a suspension. The suspension was filtered and washed with methanol (20 mL) to give 2-(2,6-dioxo-piperidin-3-yl)-4-(furan-2-ylmethoxy)-isoindole-1,3-dione as a yellow solid (310 mg, 44 % yield): mp, 184-186 °C; ^{1}H NMR (DMSO-d_6) δ 1.99-2.04 (m, 1H, CH*H*), 2.42-2.61 (m, 2H, CH_2), 2.80-2.95 (m, 1H, CH*H*), 5.07 (dd, J = 5, 13 Hz, 1H, NC*H*), 5.35 (s, 2H, CH_2), 6.49 (dd, J = 2, 3 Hz, 1H, Ar), 6.68 (d, J = 8 Hz, 1H, Ar), 7.47 (d, J = 7 Hz, 1H, Ar), 7.68-7.71 (m, 2H, Ar), 7.83 (t, *J* = 8 Hz, 1H, Ar), 11.10 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.96, 30.93, 48.77, 62.55, 110.72, 111.38, 115.72, 116.64, 120.35, 133.35, 136.89, 143.99, 149.15, 155.12, 165.21, 166.73, 169.88, 172.76; Anal Calcd for $C_{18}H_{14}N_2O_6$ + 0.1 H_2O: C, 60.71; H, 4.02; N, 7.87; H_2O, 0.51. Found: C, 60.47; H, 3.97; N, 7.73; H_2O, 0.38.

Example 20

4-(3-Chloro-benzo[b]thiophen-2-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[219] To a solution of 3-chloro-benzo[b]thiophene-2-carboxylic acid (3.5 g, 16.6 mmol) in THF (40 mL) at 0°C was added drop-wise 1 M borane in THF (33 mL, 33.2 mmol) via a dropping funnel. The mixture was stirred at r.t overnight. The reaction was quenched with drop-wise addition of water (6 mL). Solvent was evaporated in vacuo and

the residue was partitioned between sat. sodium carbonate and ethyl acetate. The aqueous phase was extracted with ethyl acetate (100 mL), the combined organic phases was washed with water (3 x 100 mL), dried and concentrated to give (3-chloro-benzo[b]thiophen-2-yl)-methanol as a light yellow solid (3.4 g, 103% crude yield); ^{1}H NMR (DMSO-d_6) δ 4.8 (d, J = 5.8 Hz, 2H, CH_2OH), 5.87 (t, J = 5.8 Hz, 1H, CH_2OH), 7.42-8.04 (m, 4H, Ar). The product was used in the next step without further purification.

Step 2:

[220] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.0 g, 4.8 mmol), (3-chloro-benzo[b]thiophen-2-yl)-methanol (1.9 g, 9.5 mmol), and polymer-supported triphenyl phosphine (3.0 g, 9.5 mmol) in THF (30 mL) in an ice-bath was slowly added diisopropyl azodicarboxylate (1.9 mL, 9.5 mmol) and stirred at r.t. overnight. The mixture was filtered and the solid was washed with ethyl acetate (10 mL). The filtrate was evaporated and the residue was purified by flash column chromatography (EtOAc/Hexane) to give 3-(3-chloro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid dimethyl ester (2.1 g, 109% crude yield). The product was used in the next step without further purification.

Step 3:

[221] A solution of 3-(3-chloro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid dimethyl ester (1.9 g, 4.8 mmol) in reagent alcohol (120 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(3-chloro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid as an off-white solid (1.6 g, 92% yield). The product was used in the next step without further purification.

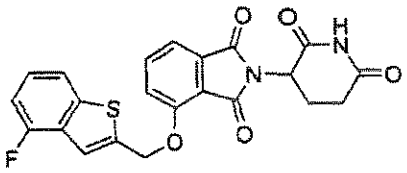
Step 4:

[222] A mixture of 3-(3-chloro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid (1.6 g, 4.4 mmol), alpha-amino-glutarimide hydrochloride (0.76 g, 4.6 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(3-chloro-benzo[b]thiophen-2-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (0.76 g, 38% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1% H_3PO_4, 5.26 min (98.7%); mp, 240-242°C; ^{1}H NMR (DMSO-d_6) δ 2.02-2.06 (m, 1H, CH*H*), 2.54-2.62 (m, 2H, CH_2), 2.83-2.95 (m, 1H, CH*H*), 5.10 (dd, J = 6, 12 Hz, 1H, C*H*), 5.74 (s, 2H, CH_2), 7.49-8.10 (m, 7H, Ar), 11.12 (s, 1H, N*H*); ^{13}C

NMR (DMSO-d_6) δ 21.94, 30.90, 48.79, 63.99, 116.26, 116.98, 118.36, 120.46, 121.39, 123.36, 125.57, 126.19, 132.93, 133.34, 135.42, 136.91, 137.04, 154.62, 165.05, 166.64, 169.85, 172.73. Anal Calcd For $C_{22}H_{15}N_2O_5SCl$ + 0.1 H_2O: C, 58.09; H, 3.32; N, 6.16; S, 7.05; Cl, 7.79. Found: C, 57.77; H, 3.06; N, 6.08; S, 6.87; Cl, 8.05.

Example 21

2-(2,6-Dioxo-piperidin-3-yl)-4-(4-fluoro-benzo[b]thiophen-2-ylmethoxy)-isoindole-1,3-dione



Step 1:

[223] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.1 g, 5.2 mmol), (4-fluoro-benzo[b]thiophen-2-yl)-methanol (0.96 g, 10.5 mmol), and polymer-supported triphenyl phosphine (3.0 g, 10.5 mmol) in THF (35 mL) in an ice-bath was slowly added diisopropyl azodicarboxylate (2.1 mL, 10.5 mmol) and stirred at r.t. overnight. The mixture was filtered and the solid was washed with ethyl acetate (10 mL). The filtrate was evaporated and the residue was purified by flash column chromatography (EtOAc/Hexane) to give 3-(4-fluoro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid dimethyl ester (1.5 g, 76% yield). The product was used in the next step without further purification.

Step 2:

[224] A solution of 3-(4-fluoro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid dimethyl ester (1.5 g, 4.0 mmol) in reagent alcohol (120 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(4-fluoro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid as an off-white solid (1.2 g, 84% yield). The product was used in the next step without further purification.

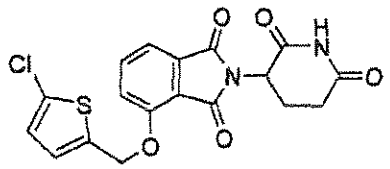
Step 3:

[225] A mixture of 3-(4-fluoro-benzo[b]thiophen-2-ylmethoxy)-phthalic acid (1.2 g, 3.4 mmol), alpha-amino-glutarimide hydrochloride (0.58 g, 3.6 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 2-(2,6-dioxo-piperidin-3-

yl)-4-(4-fluoro-benzo[b]thiophen-2-ylmethoxy)-isoindole-1,3-dione as a white solid (0.66 g, 44% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1% H_3PO_4, 3.08 min (97.5%); mp, 264-266°C; ^1H NMR (DMSO-d_6) δ 2.01-2.08 (m, 1H, CH*H*), 2.54-2.95 (m, 2H, CH*HC*H_2), 5.11 (dd, J = 6, 12 Hz, 1H, C*H*), 5.73 (s, 2H, CH_2), 7.18-7.88 (m, 7H, Ar), 11.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.98, 30.95, 48.82, 65.85, 109.57, 109.81, 116.04, 116.91, 118.02, 119.02, 119.07, 120.37, 125.98, 126.08, 127.39, 127.65, 133.38, 137.02, 140.81, 141.98, 142.06, 154.81, 155.10, 158.41, 165.17, 166.71, 169.91, 172.78. Anal Calcd For $C_{22}H_{15}N_2O_5SF$: C, 60.27; H, 3.45; N, 6.39; S, 7.31; F, 4.33. Found: C, 60.40; H, 3.26; N, 6.29; S, 7.24; F, 4.32.

Example 22

4-(5-Chloro-thiophen-2-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione



Step 1:

[226] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.4 g, 6.8 mmol) in acetone (70 mL) and potassium carbonate (2.8 g, 20 mmol) was added 2-chloro-5-chloromethyl-thiophene (0.83 mL, 7.1 mmol) and refluxed for two hours. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL) and washed with water (2 x 100 mL). The combined organic phases was dried, concentrated and purified by flash column chromatography (EtOAc/Hexane) to give 3-(5-chloro-thiophen-2-ylmethoxy)-phthalic acid dimethyl ester (2.3 g, 100% crude yield). The product was used in the next step without further purification.

Step 2:

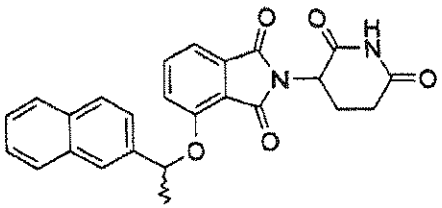
[227] A solution of 3-(5-chloro-thiophen-2-ylmethoxy)-phthalic acid dimethyl ester (2.3 g, 6.7 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (60 mL) was refluxed for two hours. The solution was evaporated and the residue was dissolved in water (100 mL) and washed with methylene chloride (3 x 100 mL) then acidified to pH around 4. The resulting mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers was washed with water (2 x 100 mL), dried and concentrated to give 3-(5-chloro-thiophen-2-ylmethoxy)-phthalic acid as an off-white solid (1.6 g, 76% yield). The product was used in the next step without further purification.

Step 3:

[228] A mixture of 3-(5-chloro-thiophen-2-ylmethoxy)-phthalic acid (1.6 g, 5.1 mmol), alpha-amino-glutarimide hydrochloride (0.88 g, 5.4 mmol) in pyridine was refluxed overnight. The mixture was evaporated and the residue was purified by flash column chromatography (methanol/methylene chloride) to give 4-(5-chloro-thiophen-2-ylmethoxy)-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione as a white solid (0.76 g, 36% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1% H_3PO_4, 2.63 min (99.3%); mp, 217-219°C; ^{1}H NMR (DMSO-d_6) δ 2.01-2.07 (m, 1H, CH*H*), 2.54-2.57 (m, 2H, CH_2), 2.62-2.95 (m, 1H, CH*H*), 5.10 (dd, J = 6, 12 Hz, 1H, C*H*), 5.50 (s, 2H, CH_2), 7.07-7.87 (m, 5H, Ar), 11.11 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.93, 30.90, 48.75, 65.38, 115.94, 116.80, 120.44, 126.55, 127.83, 129.09, 133.31, 136.93, 137.54, 154.76, 165.14, 166.68, 169.77, 169.86, 172.73. Anal Calcd For $C_{18}H_{13}N_2O_5SCl$: C, 53.41; H, 3.24; N, 6.92; S, 7.92%; Cl, 8.76. Found: C, 53.39; H, 2.95; N, 6.80; S, 7.62%; Cl, 9.01.

Example 23

2-(2,6-Dioxo-piperidin-3-yl)-4-(1-naphthalen-2-yl-ethoxy)-isoindole-1,3-dione



Step 1:

[229] A mixture of polymer-supported PPh_3 (3.1 g, ~ 9.5 mmol) and α-methyl-2-naphthalenemethanol (0.82 g, 4.8 mmol) in 20 mL THF was cooled to 0 °C under N_2. Diisopropylazodicarboxylate (1.9 g, 9.5 mmol) was added dropwise, and subsequently 3-hydroxy-phthalic acid dimethyl ester (1.0 g, 4.8 mmol) was added as a solid. The mixture stirred for an additional hour at 0 °C and was then allowed to warm to room temperature. After stirring for 16 h, the mixture was filtered. The filter was washed with ethyl acetate (20 mL) and the combined filtrates were evaporated. The residue was chromatographed in hexanes-ethyl acetate gradient, eluting 1.2 g of the 3-(1-naphthalen-2-yl-ethoxy)-phthalic acid dimethyl ester at 20-30% ethyl acetate, in 66% yield; ^{1}H NMR (DMSO-d_6) δ 1.70 (d, J = 6.5 Hz, 3H), 3.88 (s, 3H), 4.03 (s, 3H), 5.49 (q, J = 6.5 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.42-7.53 (m, 4H), 7.76-7.84 (m, 4H).

Step 2:

[230] A mixture of 3-(1-naphthalen-2-yl-ethoxy)-phthalic acid dimethyl ester (0.9 g, 2.5 mmol) and 3N NaOH (50 mL) in ethanol (100 mL) was heated to reflux for 2 h. The

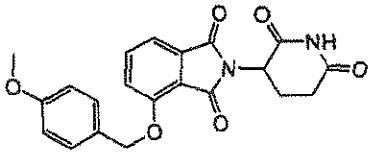
mixture was cooled and the solvent was removed under vacuum. The residue was dissolved in water (100 mL) and washed with CH_2Cl_2 (3 x 100 mL), acidified (HCl), and extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were washed with water (3 x 75 mL), dried ($MgSO_4$), and evaporated, providing 0.50 g of 3-(1-naphthalen-2-yl-ethoxy)-phthalic acid, in 60% yield; ^{1}H NMR (DMSO-d_6) δ 1.60 (d, J = 6.2 Hz, 3H), 5.79 (q, J = 6.2 Hz, 1H), 7.21-7.31 (m, 2H), 7.38 (dd, J = 7.1 Hz, J = 1.3 Hz, 1H), 7.46-7.57 (m, 3H), 7.83-7.93 (m, 4H).

Step 3:

[231] A mixture of 3-(1-naphthalen-2-yl-ethoxy)-phthalic acid (0.36 g, 1.0 mmol) and *rac*-α-aminoglutarimide hydrochloride (0.16 g, 1.0 mmol) in pyridine (10 mL) was heated to reflux for 16 h. The mixture was cooled and evaporated under vacuum. The residue was dissolved in ethyl acetate (100 mL) and washed with dilute aqueous HCl (2 x 100 mL) and water (100 mL), and was evaporated. The residue was chromatographed using a CH_2Cl_2-methanol gradient, eluting the product at 95:5 CH_2Cl_2-methanol, 0.27 g, in 64% yield; mp 174-176 °C; HPLC, Waters Symmetry C-18, 3.9 x 150 mm, 5 μm, 1 mL/min, 240 nm, 60/40 CH_3CN/0.1 % H_3PO_4, 3.69 (99.65%); ^{1}H NMR (DMSO-d_6) δ 1.71 (d, J = 6.0 Hz, 3H), 1.99-2.09 (m, 1H), 2.51-2.65 (m, 2H), 2.84-2.97 (m, 1H), 5.13 (dd, J = 12.5 Hz, J = 5.3 Hz, 1H), 6.00 (q, J = 6.0 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 7.44-7.53 (m, 3H), 7.62 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 7.9 Hz, 1H), 7.87-7.96 (m, 3H), 8.00 (s, 1H), 11.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0, 23.7, 31.0, 48.8, 76.5, 115.5, 117.2, 121.5, 123.6, 124.5, 126.2, 126.4, 127.6, 127.8, 128.5, 132.5, 132.7, 133.4, 136.7, 139.4, 154.8, 165.3, 166.7, 170.0, 172.8; Anal. Calcd for $C_{25}H_{20}N_2O_5$: C, 70.08; H, 4.71; N, 6.54. Found: C, 69.71; H, 4.51; N, 6.28.

Example 24

2-(2,6-Dioxo-piperidin-3-yl)-4-(4-methoxy-benzyloxy)-isoindole-1,3-dione



Step 1:

[232] A stirred mixture of 3-hydroxyphthalic anhydride (20.5 g, 125 mmol) in methanol (100 mL) was heated to reflux for three hours. The solvent was evaporated *in vacuo*, and the residue was suspended in sodium bicarbonate (29.4 g, 350 mmol) in DMF (250 mL), followed by addition of iodomethane (19 mL, 300 mmol) and heating at 55°C for four hours. The mixture was cooled to room temperature, solvent evaporated *in vacuo*, and

the residue was partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was washed with water (2 x 200 mL), dried, concentrated *in vauco*, and then purified by flash column chromatography (Silica Gel, EtOAc/Hexane, 0% gradient to 100% 30 min) to give 3-hydroxyphthalic acid dimethyl ester (20.2 g, 77% yield). The product was used in the next step without further purification.

Step 2:

[233] To a stirred suspension of 3-hydroxyphthalic acid dimethyl ester (1.1 g, 5.2 mmol) in acetone (45 mL) and potassium carbonate (2.2 g, 15.7 mmol), was added 1-bromomethyl-4-methoxy-benzene (0.79 mL, 5.5 mmol). The mixture was refluxed for six hours. The solvent was evaporated *in vacuo*, and the residue was partitioned between water (50 mL) and ethyl acetate (80 mL). The organic layer was washed with water (2 x 50 mL), dried, concentrated *in vacuo*, and purified by flash column chromatography (Silica Gel, EtOAc/Hexane, 0% gradient to 100% 30 min) to give 3-(4-methoxy-benzyloxy)-phthalic acid dimethyl ester (2.0 g, 115% crude yield). The product was used in the next step without further purification.

Step 3:

[234] A stirred solution of 3-(4-methoxy-benzyloxy)-phthalic acid dimethyl ester (2.0 g crude, 5.5 mmol) in reagent alcohol (100 mL) and 3 N sodium hydroxide (35 mL) was refluxed for two hours. The solution was evaporated *in vacuo*, and the residue was dissolved in water (80 mL) and washed with methylene chloride (3 x 70 mL), then acidified to pH around 4 by HCl. The resulting mixture was extracted with ethyl acetate (2 x 60 mL), and the combined organic layers was washed with water (2 x 70 mL), dried, and concentrated *in vacuo* to give 3-(4-methoxy-benzyloxy)-phthalic acid as an off-white solid (1.6 g, 100% crude yield). The product was used in the next step without further purification.

Step 4:

[235] A stirred mixture of 3-(4-methoxy-benzyloxy)-phthalic acid (1.5 g, 5.2 mmol), alpha-amino-glutarimide hydrochloride (0.90 g, 5.4 mmol) in pyridine was refluxed overnight. The mixture was evaporated *in vacuo*, and the residue was purified by flash column chromatography (Silica Gel, methanol/methylene chloride, 0% gradient to 10% 30 min) to give 2-(2,6-dioxo-piperidin-3-yl)-4-(4-methoxy-benzyloxy)-isoindole-1,3-dione as a white solid (0.83 g, 40% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 50/50 CH_3CN/0.1% H_3PO_4, RT = 4.17 min (98.6%); mp, 178-180°C; ^{1}HNMR (DMSO-d_6) δ1.99-2.06 (m, 1H, CH*H*), 2.51-2.82 (m, 2H, CH*H*CH_2), 3.76 (s, 3H,

CH_3), 5.08 (dd, J = 6, 12 Hz, 1H, C*H*), 5.29 (s, 2H, CH_2), 6.95-7.84 (m, 7H, Ar), 11.11 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.96, 30.91, 48.72, 55.08, 69.92, 113.88, 115.41, 116.55, 120.29, 127.93, 129.21, 133.25, 136.92, 155.57, 159.10, 165.28, 166.77, 169.90, 172.75. Anal Calcd For $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.86; H, 4.30; N, 6.92.

5.1 ASSAYS

5.1.1 TNFα Inhibition Assay in PMBC

[236] 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 μg/ml streptomycin (Life Technologies).

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

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

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

minutes at 4°C. Purified T cells are removed from beads using a Dynal magnet. Typical yield is about 50% T cells, 87-95% $CD3^+$ by flow cytometry.

[239] Tissue culture 96-well flat-bottom plates are coated with anti-CD3 antibody OKT3 at 5 μg/ml in PBS, 100 μl per well, incubated at 37°C for 3-6 hours, then washed four times with complete medium 100 μl/well just before T cells are added. Compounds are diluted to 20 times of final in a round bottom tissue culture 96-well plate. Final concentrations are about 10 μM to about 0.00064 μM. A 10 mM stock of compounds provided herein is diluted 1:50 in complete for the first 20x dilution of 200 μM in 2 % DMSO and serially diluted 1:5 into 2 % DMSO. Compound is added at 10 μl per 200 μl culture, to give a final DMSO concentration of 0.1 %. Cultures are incubated at 37°C, 5 % CO_2 for 2-3 days, and supernatants analyzed for IL-2 and MIP-3α by ELISA (R&D Systems). IL-2 and MIP-3α 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).

5.1.3 Cell Proliferation Assay

[240] 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.

[241] 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 μM 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 37°C 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 μl/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).

5.1.4 Immunoprecipitation and Immunoblot

[242] Namalwa cells are treated with DMSO or an amount of a compound provided herein for 1 hour, then stimulated with 10 U/ml of Epo (R&D Systems) for 30 minutes. Cell lysates are prepared and either immunoprecipitated with Epo receptor Ab or separated immediately by SDS-PAGE. Immunoblots are probed with Akt, phospo-Akt (Ser473 or Thr308), phospho-Gab1 (Y627), Gab1, IRS2, actin and IRF-1 Abs and analyzed on a Storm 860 Imager using ImageQuant software (Molecular Dynamics).

5.1.5 Cell Cycle Analysis

[243] Cells are treated with DMSO or an amount of a compound provided herein overnight. Propidium iodide staining for cell cycle is performed using CycleTEST PLUS (Becton Dickinson) according to manufacturer's protocol. Following staining, cells are analyzed by a FACSCalibur flow cytometer using ModFit LT software (Becton Dickinson).

5.1.6 Apoptosis Analysis

[244] Cells are treated with DMSO or an amount of a compound provided herein at various time points, then washed with annexin-V wash buffer (BD Biosciences). Cells are incubated with annexin-V binding protein and propidium iodide (BD Biosciences) for 10 minutes. Samples are analyzed using flow cytometry.

5.1.7 Luciferase Assay

[245] Namalwa cells are transfected with 4 μg of AP1-luciferase (Stratagene) per 1 x 10^6 cells and 3 μl Lipofectamine 2000 (Invitrogen) reagent according to manufacturer's instructions. Six hours post-transfection, cells are treated with DMSO or an amount of a compound provided herein. Luciferase activity is assayed using luciferase lysis buffer and substrate (Promega) and measured using a luminometer (Turner Designs).

5.1.8 TNFα Inhibition and IL-2 Production

[246] Using procedures substantially similar to those provided in Section 5.1.1 above, IC_{50} values for certain of the compounds provided herein for TNFα inhibition were determined. The determined IC_{50} values ranged from less than 0.2 nM to about 10-100 μM. These results show that compounds provided herein are useful as inhibitors of TNFα.

[247] Using procedures substantially similar to those described in Section 5.1.2. above, EC_{50} values of certain compounds provided herein for the production of IL-2 were also determined. The determined EC_{50} values ranged from greater than 1 nM to less than 1 μM. These results show that compounds provided herein are useful as stimulators of IL-2 production.

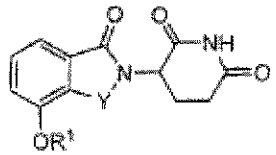
[248] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to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

[249] 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 to the claimed subject matter. The full scope of the invention is better understood with reference to the appended claims.

CLAIMS

What is claimed is:

1. A compound of formula:



or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof, wherein:
Y is CH_2; and
R^1 is heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl or heterocyclylcarbonyl;
and where R^1 is optionally substituted with one or more groups selected from alkoxy, halo, alkyl, carboxy, alkylaminocarbonyl, alkoxycarbonyl, nitro, amine, nitrile, haloalkyl, hydroxy, and alkylsulfonyl.

2. The compound of claim 1, wherein R^1 is heteroarylalkyl.

3. The compound of any of claims 1-2, wherein the heteroaryl group in R^1 is a 5 or 6 membered monocyclic heteroaryl group containing 1 -3 heteroatoms selected from O, N and S.

4. The compound of any of claims 1-3, wherein the heteroaryl group in R^1 is a bicyclic aryl or bicyclic heteroaryl group.

5. The compound of any of claims 1-4, wherein R^1 is substituted with one or more substituents selected from alkoxy, halo, alkyl and alkylsulfonyl.

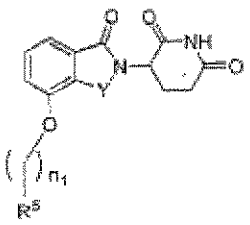
6. The compound of any of claims 1-5, wherein R^1 substituted with one or two substituents selected from methoxy, chloro, bromo, fluoro, methyl and methylsulfonyl.

7. The compound of any of claims 1-4, wherein R^1 is substituted with one or more substituents selected from nitro, amino, haloalkyl, nitrile, or hydroxy.

8. The compound of claim 1, wherein R^1 is quinolylmethyl, benzofurylmethyl, benzothienylmethyl, furylmethyl or thienylmethyl.

9. The compound of claim 1, wherein R^1 is 3 -quinolylmethyl, 2-quinolylmethyl, 2-benzofurylmethyl, 2-benzothienylmethyl, 3-chlorothien-2-ylmethyl, 4-fluorobenzothien-2-ylmethyl, 2-furylmethyl, 5-chlorothien-2-ylmethyl or 1-naphth-2-ylethyl.

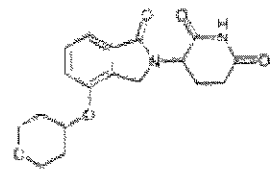
10. The compound of claim 1, wherein the compound has formula:

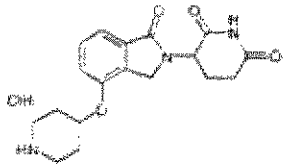


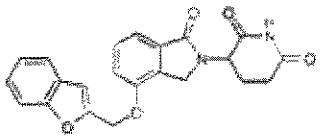
and wherein R^5 is heteroaryl, optionally substituted with one, two or three groups selected from alkyl, halo, alkoxy, carboxy, alkylaminocarbonyl, alkoxycarbonyl, nitro, amine, nitrile, haloalkyl, hydroxy, and alkylsulfonyl; and n_1 is 0-5.

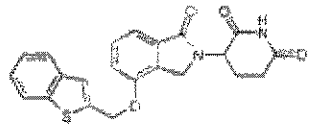
11. The compound of claim 10, wherein R^5 is selected from furyl, thienyl, benzofuryl, benzothienyl and quinolyl, optionally substituted with one or two groups selected from methyl, methoxy, chloro, fluoro, bromo and methylsulfonyl.

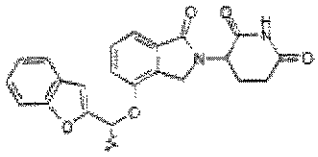
12. The compound of claim 1, selected from the group consisting of:



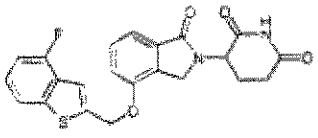








and



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

14. A single unit dosage form comprising a compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

15. The single unit dosage form of claim 14, which is suitable for oral or parenteral administration.

16. The single unit dosage form of claim 15, which is suitable for oral administration.

17. The single unit dosage form of claim 16, which is a tablet or a capsule.

ABSTRACT

4'-O-SUBSTITUTED ISOINDOLINE DERIVATIVES AND COMPOSITIONS COMPRISING AND METHODS OF USING THE SAME

Provided are 4'-0 substituted isoindoline compounds of formula (1), and pharmaceutically acceptable salts, solvates, clathrates, stereoisomers, and prodrugs thereof. Methods of use, and pharmaceutical compositions of these compounds are disclosed.

Not available