[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.

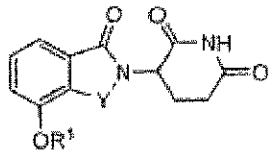
[12] Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, hepain and steroids have been proposed to be useful in the treatment of certain specific diseases. Taylor *et al.*, *Nature* 297:307 (1982); 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.

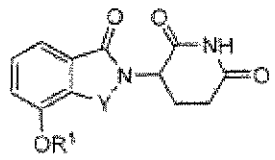
[20] In other embodiments, a compound provided herein, or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof, is administered in combination with another drug ("second active agent") or treatment. Second active agents include small molecules and large molecules (*e.g.*, 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.

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 ~~hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,~~ heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, ~~arylaminocarbonyl, alkylcarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, cycloalkylcarbonyl,~~ 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 ~~aryl, aralkyl or~~ heteroarylalkyl.

~~3. The compound of any of claims 1-2, wherein the aryl group in R^1 is a 5 or 6 membered monocyclic aryl group.~~

34. The compound of any of claims 1-2~~3~~, 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.

45. The compound of any of claims 1-34, wherein the heteroaryl group in R^1 is a bicyclic aryl or bicyclic heteroaryl group.

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

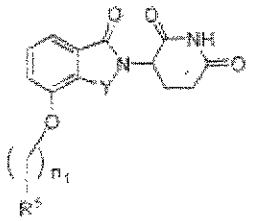
67. The compound of any of claims 1-5~~6~~, wherein R^1 substituted with one or two substituents selected from methoxy, chloro, bromo, fluoro, methyl and methylsulfonyl.

78. The compound of any of claims 1-4~~5~~, wherein R^1 is substituted with one or more substituents selected from nitro, amino, haloalkyl, nitrile, or hydroxy.

89. The compound of claim 1, wherein R^1 is ~~phenyl, benzyl, naphthylmethyl,~~ quinolylmethyl, benzofurylmethyl, benzothienylmethyl, furylmethyl or thienylmethyl.

910. The compound of claim 1, wherein 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 l-naphth-2-ylethyl.

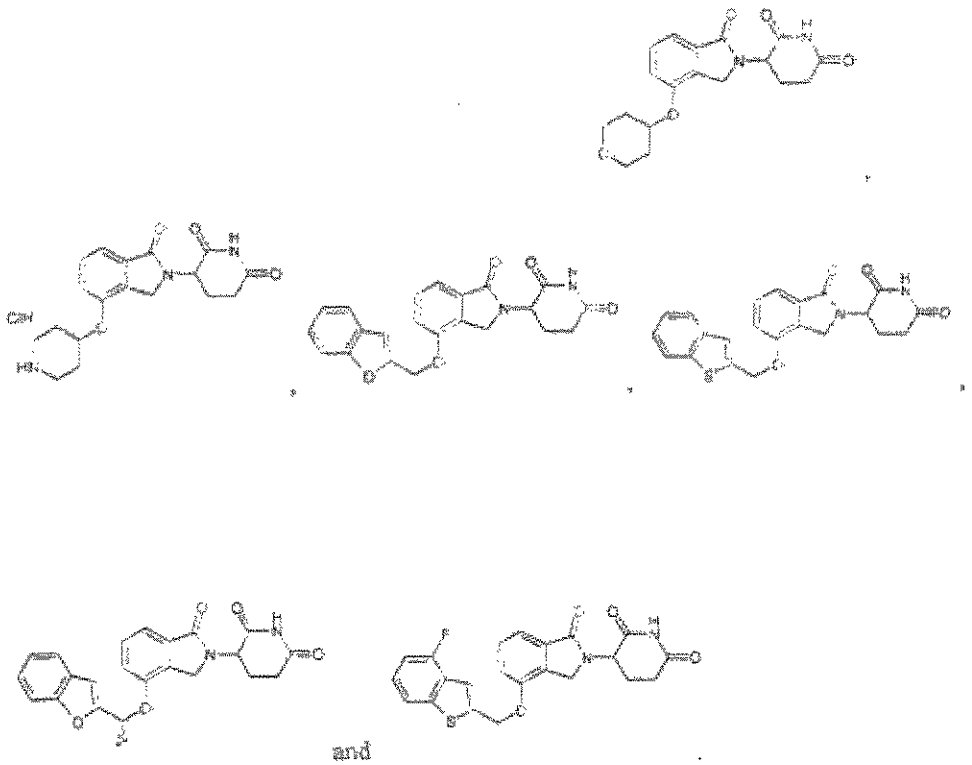
1011. The compound of claim 1, wherein the compound has formula:



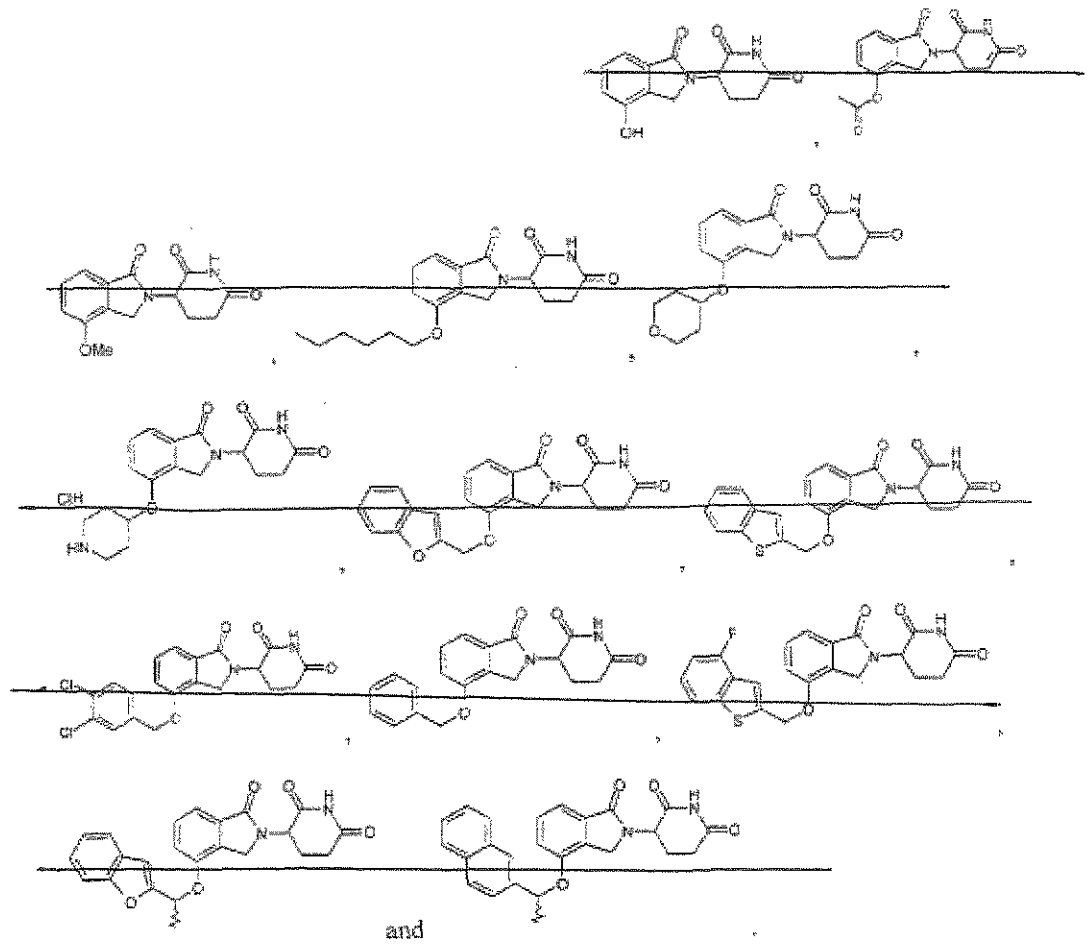
and wherein R^5 is ~~aryl or~~ heteroaryl, optionally substituted with one, two or three groups selected from alkyl, halo, alkoxy, carboxy, alkylaminocarbonyl, alkoxycarbonyl, nitro, amine, nitrile, haloalkyl, hydroxy, and alkylsulfonyl; and n_1 is 0-5.

1112. The compound of claim 1011, wherein 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.

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



and



and

134. A pharmaceutical composition comprising a compound of any one of claims 1-123, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

~~15. Use of a compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof in the manufacture of a medicament for treating, managing or preventing a disease or disorder, wherein the disease or disorder is cancer, a disorder associated with angiogenesis, pain, macular degeneration or a related syndrome, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis or a related disorder, dysfunctional sleep or a related disorder, an infectious disease, hemoglobinopathy or a related disorder, or a TNFα related disorder and wherein said medicament is to be administered to a patient.~~

~~16. The use of claim 15, wherein said medicament is to be administered with one or more additional active agents.~~

~~17. The use of claim 16, wherein the disease is cancer, and the additional active agent is a cancer vaccine.~~

~~18. The use of claim 16, wherein the disease is an infectious disease, and the additional active agent is a vaccine for said infectious disease.~~

~~19. The use of claim 15, wherein the medicament is to be administered orally or parenterally.~~

1420. A single unit dosage form comprising a compound of any one of claims 1-1213, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

1521. The single unit dosage form of claim 1420, which is suitable for oral or parenteral administration.

1622. The single unit dosage form of claim 1521, which is suitable for oral administration.

1723. The single unit dosage form of claim 1622, which is a tablet or a capsule.