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.

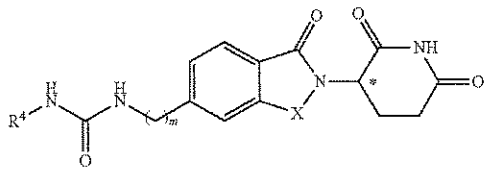
[0010] Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, heparin and steroids have been proposed to be useful in the treatment of certain specific diseases. Taylor *et al.*, *Nature* 297:307 (1982); Folkman *et al.*, *Science* 221:719 (1983); and U.S. Pat. Nos. 5,001,116 and 4,994,443.

[0011] Still, there is a significant need for effective methods of treating, preventing, and managing cancer and other diseases and conditions, particularly 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

[0011a] In a first aspect of the present disclosure, there is provided a compound of Formula II:

(II)



or a pharmaceutically acceptable salt, prodrug, or stereoisomer thereof, wherein:
X is CH_2;
m is an integer of 0, 1, 2, or 3;
R^4 is C_{3-10} cycloalkyl, 5 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, or C_{0-4} alkyl-$NR^{41}R^{42}$; wherein the cycloalkyl, heterocyclyl, and heteroaryl are each optionally substituted with one or more halogen, C_{1-6} alkyl, —CO—$NR^{43}R^{44}$, —$COOR^{45}$, or C_{0-4} alkyl-C_{6-10} aryl, wherein the aryl itself may be optionally substituted with one or more halogen; and
R^{41}, R^{42}, R^{43}, R^{44} and R^{45} are each independently hydrogen or C_{1-6} alkyl.

[0011b] In a second aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as described herein, and one or more pharmaceutically acceptable excipients or carriers.

[0012] Provided herein are isoindoline compounds, and pharmaceutically acceptable salts, solvates, prodrugs, or stereoisomers thereof.

[0013] Also provided herein are pharmaceutical compositions comprising a compound provided herein, e.g., a compound of Formula I, including a single enantiomer, a mixture of

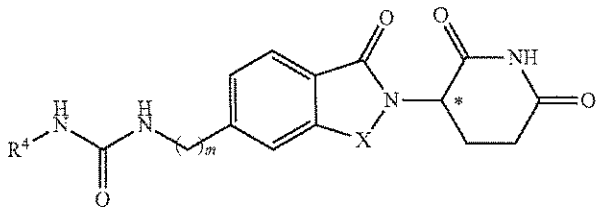
enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; in combination with one or more pharmaceutically acceptable carriers.

[0014] Further provided herein are methods of treating, preventing, or managing various diseases in a subject, which comprise administering to the subject a therapeutically effective amount of a compound provided herein, e.g., a compound of Formula I, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

What is claimed is:

1. A compound of Formula II:

(II)



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

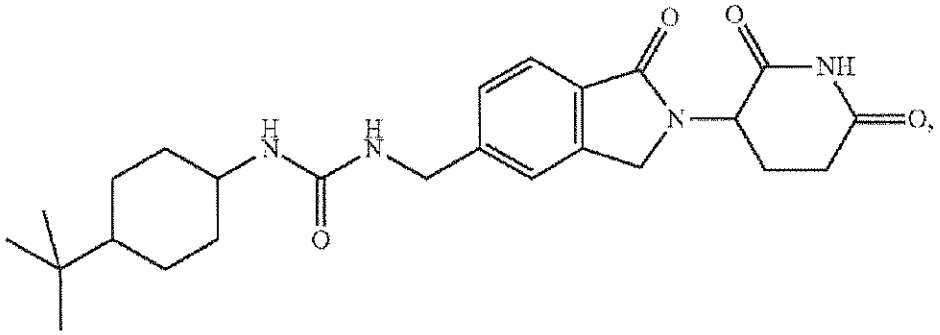
X is CH_2;

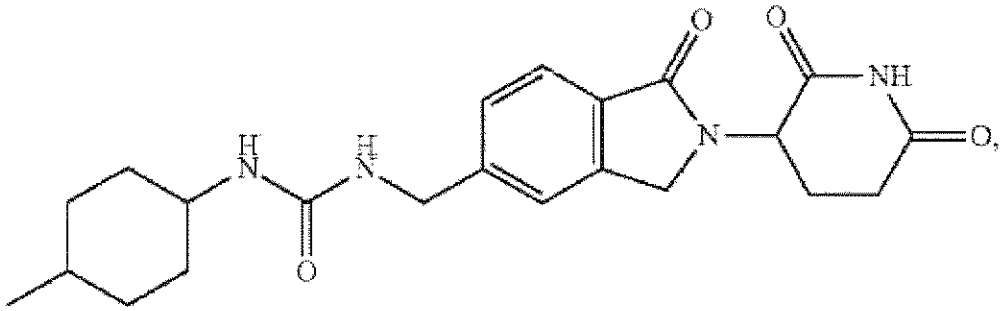
m is an integer of 0, 1, 2, or 3;

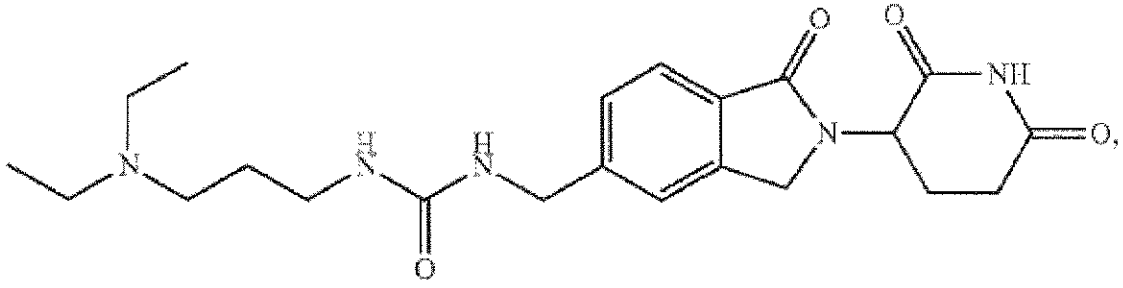
R^4 is C_{3-10} cycloalkyl, 5 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, or C_{0-4} alkyl-$NR^{41}R^{42}$; wherein the cycloalkyl, heterocyclyl, and heteroaryl are each optionally substituted with one or more halogen, C_{1-6} alkyl, —CO—$NR^{43}R^{44}$, —$COOR^{45}$, or C_{0-4} alkyl-C_{6-10} aryl, wherein the aryl itself may be optionally substituted with one or more halogen; and R^{41}, R^{42}, R^{43}, R^{44} and R^{45} are each independently hydrogen or C_{1-6} alkyl.

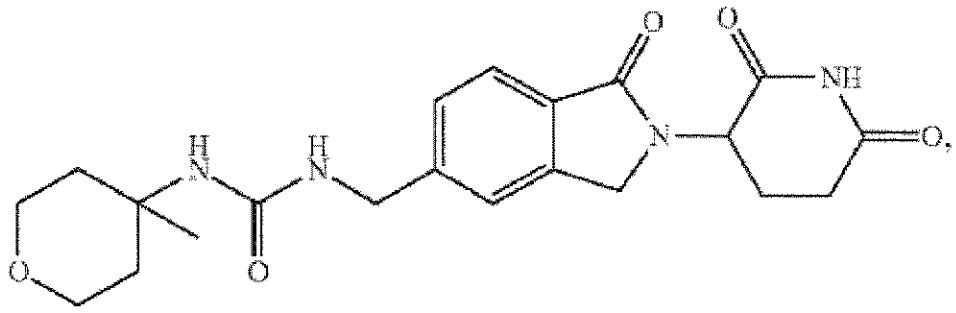
2. The compound of claim 1, wherein R^4 is 3-(N,N-diethylamino)propyl, 4-tert-butylcyclohexyl, cis-4-tert-butylcyclohexyl, trans-4-tert-butylcyclohexyl, 4-methylcyclohexyl, cis-4-methylcyclohexyl, trans-4-methylcyclohexyl, 1-benzylpiperidin-4-yl, 4-methyltetrahydro-2H-pyran-4-yl, piperidin-4-yl, 4-phenylcyclohexyl, cis-4-phenylcyclohexyl, or trans-4-phenylcyclohexyl.

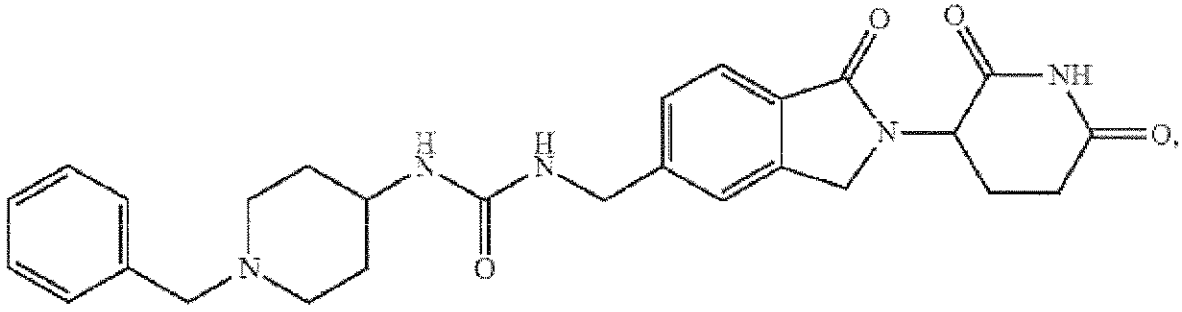
3. The compound of claim 1, which is:

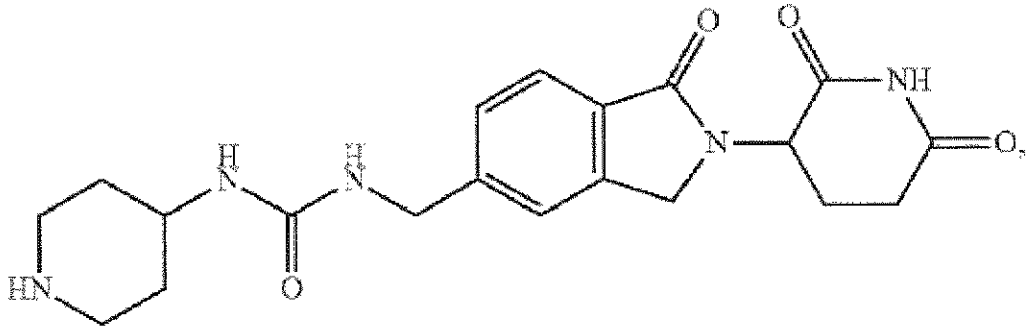


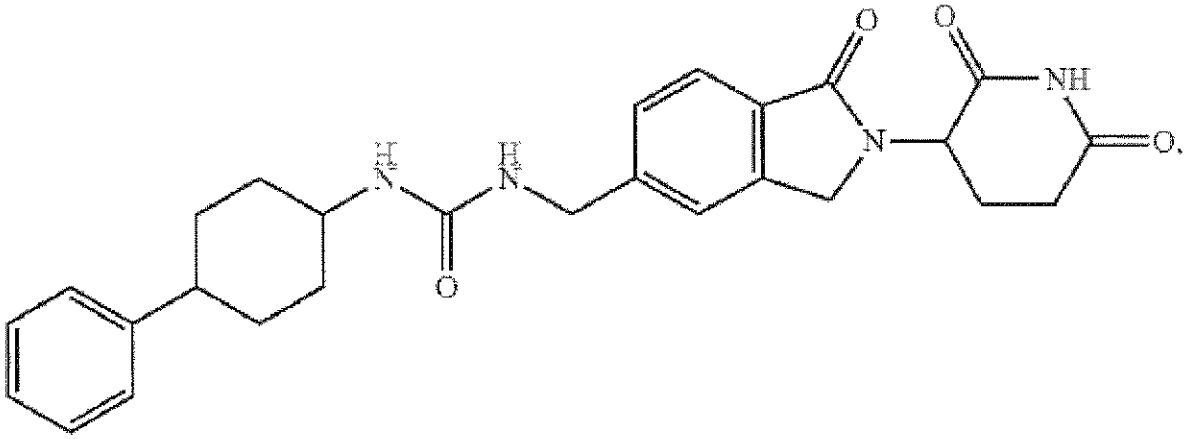


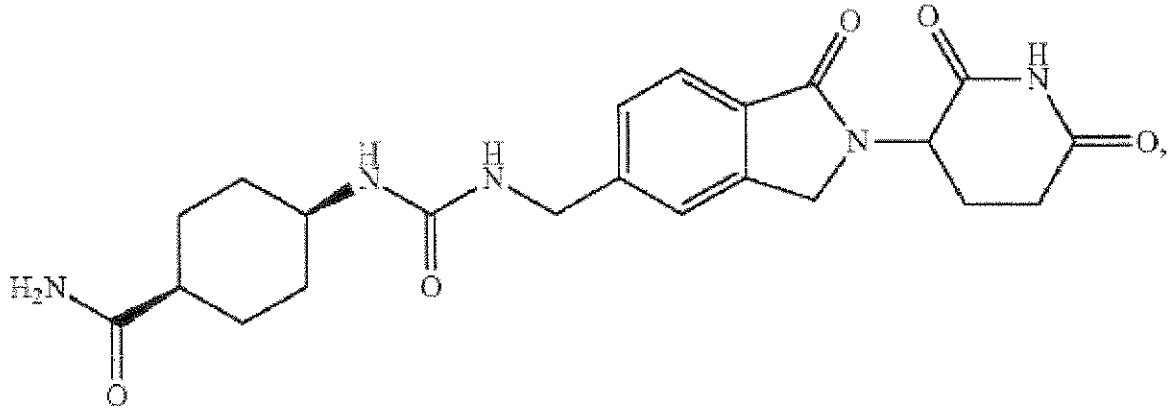


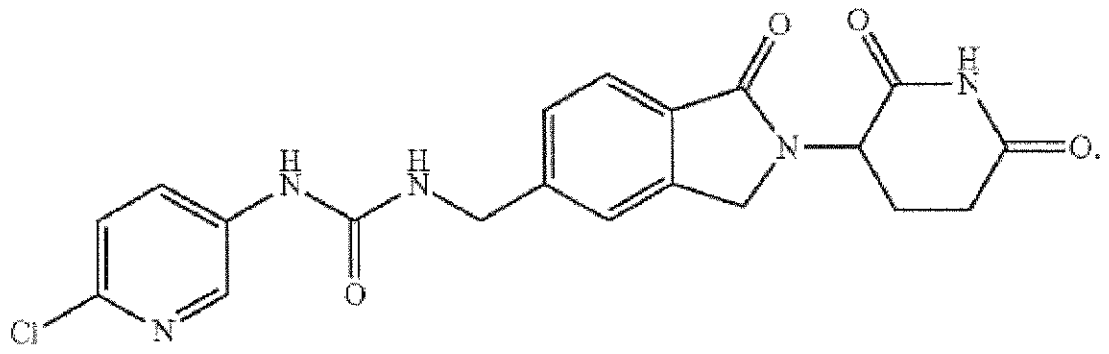


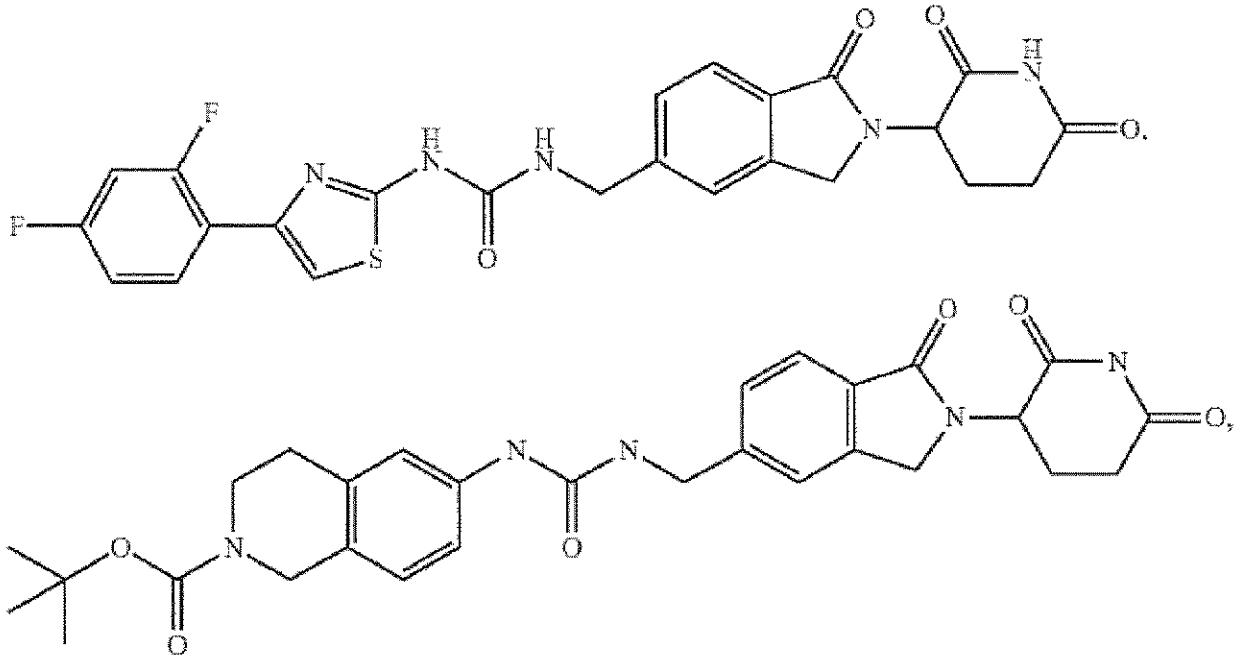












or a pharmaceutically acceptable salt, prodrug, or stereoisomer thereof.

4. A pharmaceutical composition comprising the compound of claim 1, and one or more pharmaceutically acceptable excipients or carriers.

5. The pharmaceutical composition of claim 4, further comprising a second therapeutic agent.

6. The pharmaceutical composition of claim 4, wherein the composition is formulated for single dose administration.

7. The pharmaceutical composition of claim 4, wherein the composition is formulated as oral, parenteral, or intravenous dosage form.

8. The pharmaceutical composition of claim 7, wherein the oral dosage form is a tablet or capsule.

9. The compound of claim 1, wherein X is CH_2.

10. The compound of claim 1, wherein m is 1.

11. The compound of claim 1, wherein R^4 is C_{3-10} cycloalkyl, optionally substituted with one or more (C_{1-6}) alkyl or C_{0-4} alkyl-C_{6-10} aryl.

12. The compound of claim 1, wherein R^4 is 5 to 6 membered heterocyclyl, optionally substituted with one or more (C_{1-6}) alkyl or C_{0-4}alkyl-C_{6-10} aryl.

13. The compound of claim 1, wherein R^4 is C_{0-4} alkyl-$NR^{41}R^{42}$, wherein R^{41} and R^{42} are each independently hydrogen or C_{1-6} alkyl.