cell division. Gilman *et al*., Goodman and Gilman's: *The Pharmacological Basis of Therapeutics*, Tenth Ed. (McGraw Hill, New York).

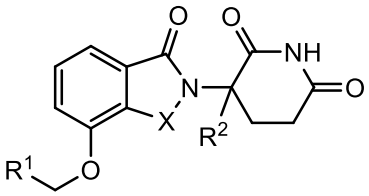
[10] Despite availability of a variety of chemotherapeutic agents, chemotherapy has many drawbacks. Stockdale, *Medicine*, vol. 3, Rubenstein and Federman, eds., ch. 12, sect. 10, 1998. Almost all chemotherapeutic agents are toxic, and chemotherapy causes significant, and often dangerous side effects 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.

[11] 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.

[12] 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

[12a] In a first aspect of the present disclosure, there is provided a compound of formula (I):



, (I)

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

X is C=O or CH_2;

R^1 is -Y-R^3;

R^2 is H or (C_1-C_6)alkyl;

Y is: heteroaryl or heterocycle, each of which may be optionally substituted with one or more halogen;

R^3 is: -$(CH_2)_n$-aryl, -O-$(CH_2)_n$-aryl or -$(CH_2)_n$-O-aryl, wherein the aryl is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano; hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen; -$(CH_2)_n$-heterocycle, -O-$(CH_2)_n$-heterocycle or -$(CH_2)_n$-O-heterocycle, wherein the heterocycle is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano; hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen; or -$(CH_2)_n$-heteroaryl, -O-$(CH_2)_n$-heteroaryl or -$(CH_2)_n$-O-heteroaryl, wherein the heteroaryl is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano; hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen; and

n is 0, 1, 2 or 3.

[12b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[12c] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition as disclosed herein, 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.

[12d] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or the pharmaceutical composition as disclosed herein for use in therapy.

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

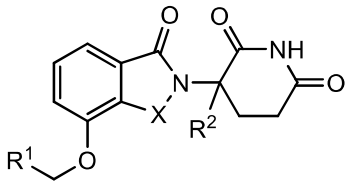
[14] Also provided are methods of treating and managing various diseases or disorders. The methods comprise administering to a patient in need of such treatment or management a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt, solvate, prodrug, clathrate, or stereoisomer thereof.

[15] Further provided are methods of preventing various diseases and disorders, which comprise administering to a patient in need of such prevention a prophylactically

CLAIMS

What is claimed is:

1. A compound of formula (I):



(I)

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

X is C=O or CH_2;

R^1 is -Y-R^3;

R^2 is H or (C_1-C_6)alkyl;

Y is: ~~6 to 10 membered aryl,~~ heteroaryl or heterocycle, each of which may be optionally substituted with one or more halogen; ~~or a bond;~~

R^3 is: -(CH_2)$_n$-aryl, -O-(CH_2)$_n$-aryl or -(CH_2)$_n$-O-aryl, wherein the aryl is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano; hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen;

-(CH_2)$_n$-heterocycle, -O-(CH_2)$_n$-heterocycle or -(CH_2)$_n$-O-heterocycle, wherein the heterocycle is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano; hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen; or

-(CH_2)$_n$-heteroaryl, -O-(CH_2)$_n$-heteroaryl or -(CH_2)$_n$-O-heteroaryl, wherein the heteroaryl is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano;

hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen; and

n is 0, 1, 2 or 3.

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

3. The compound of claim 1, wherein Y is heteroarylphenyl, and R^3 is $-(CH_2)_n$-heterocycle.

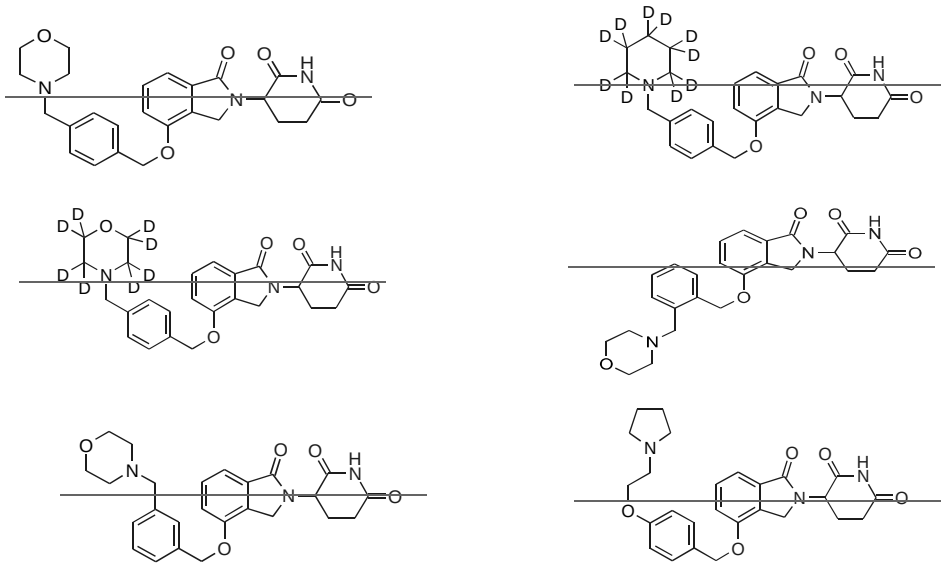
4. The compound of claim 31, wherein Y is heteroaryl, and R^3 is $-(CH_2)_n$-heterocycle.

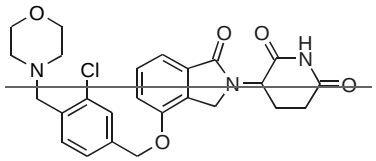
5. The compound of claim 4, wherein Y is heteroaryl, and R^3 is $-(CH_2)_n$-heterocycle, and the heterocycle is morpholinyl, piperidinyl or pyrrolidinyl.

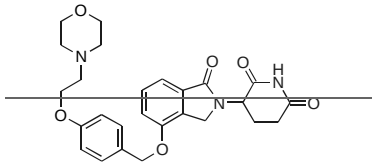
65. The compound of claim 1, wherein Y is a bondheterocycle.

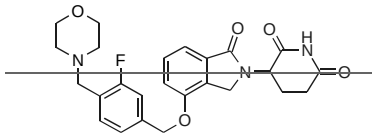
6. The compound of claim 1, wherein Y is a bond, and R^3 is $-(CH_2)_n$-heterocycle or $-(CH_2)_n$-heteroaryl.

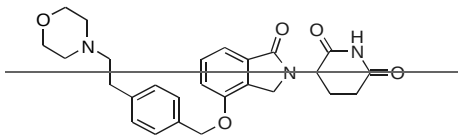
7. The compound of claim 1, which is:

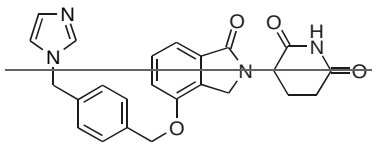


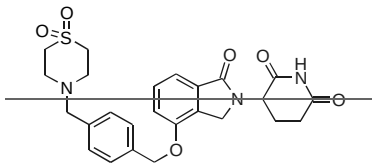


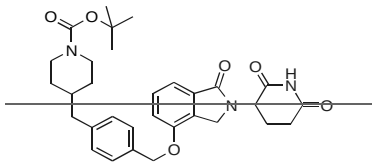


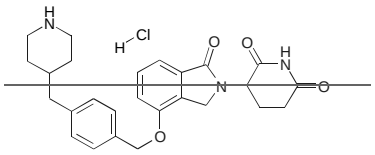


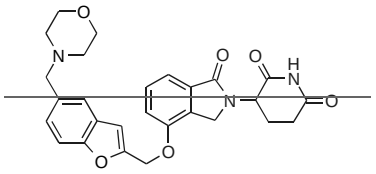


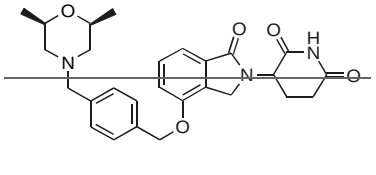


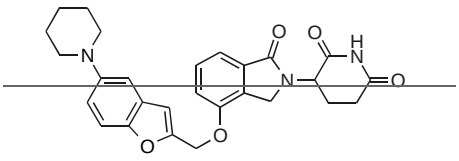


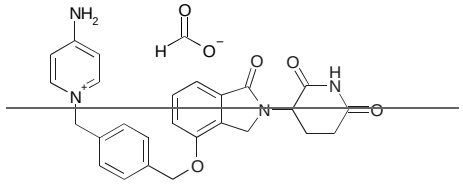


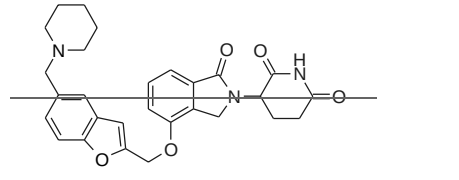


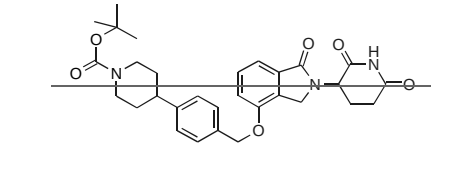


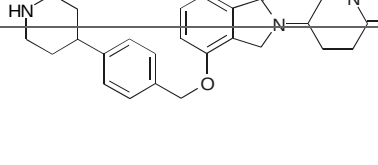


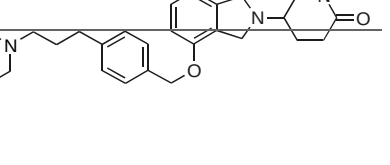


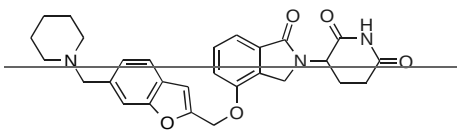


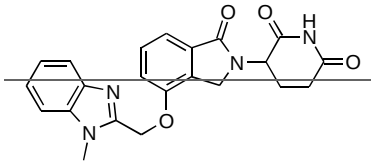


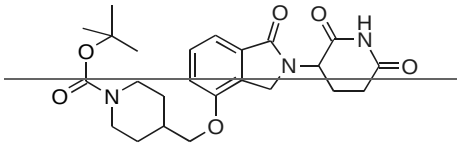


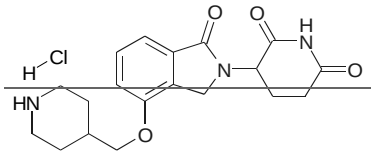


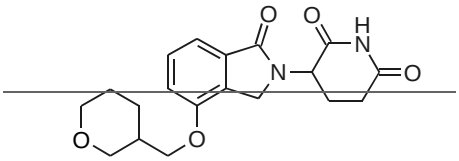


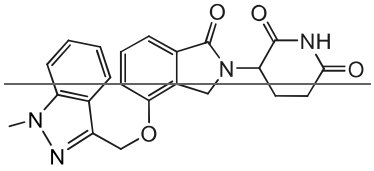


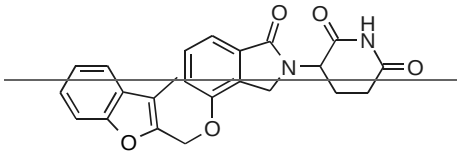


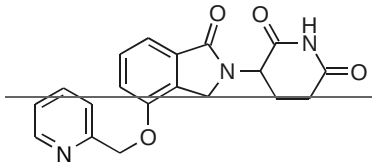


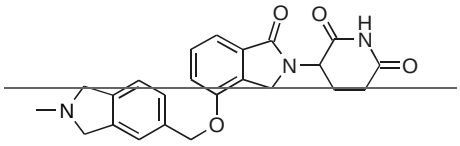


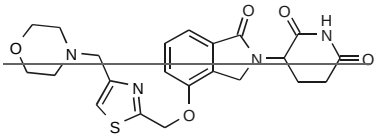


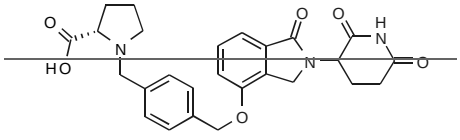


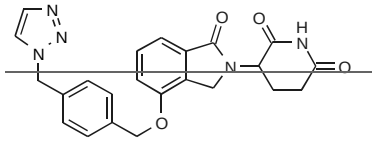


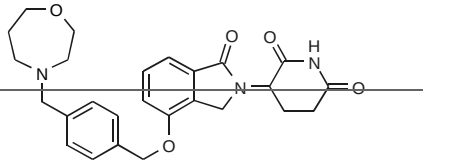


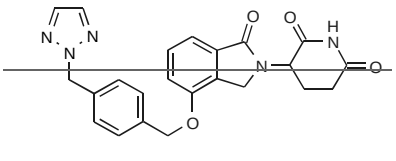


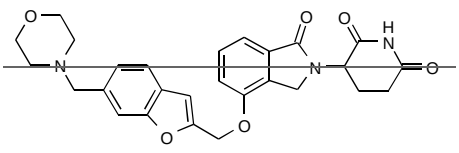


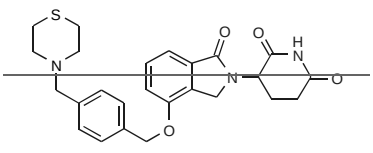


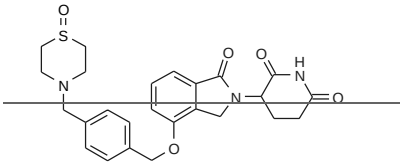


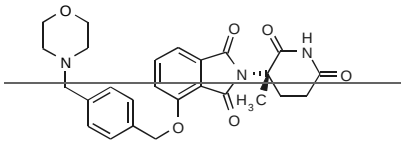


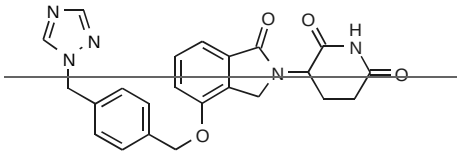


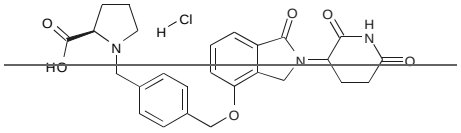


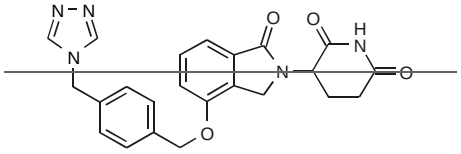


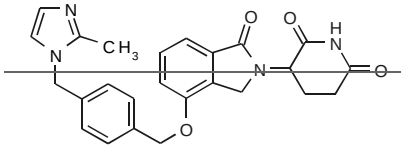


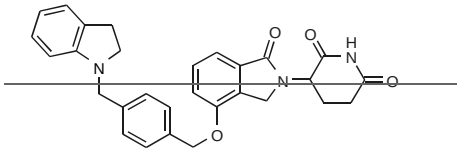


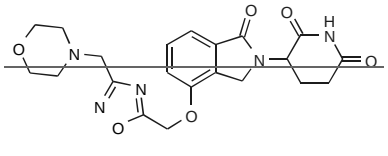


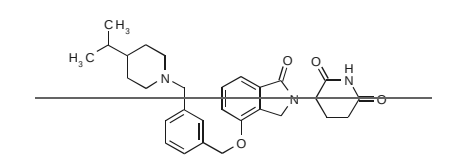


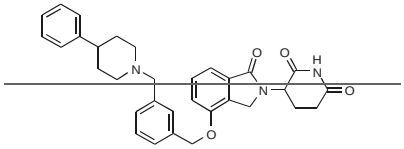


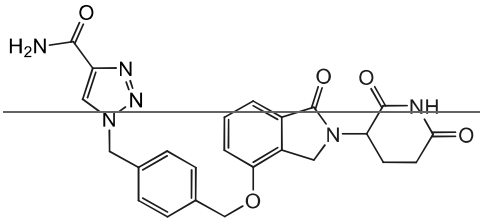


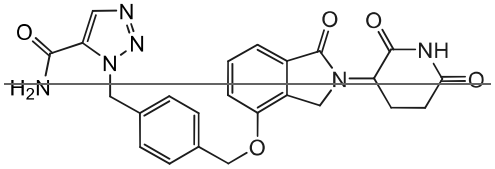


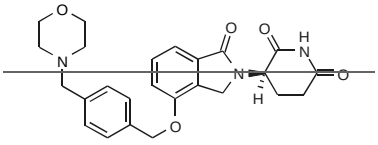


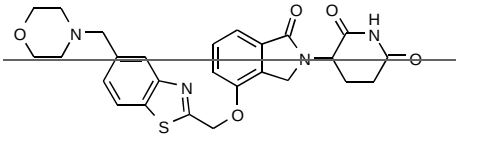


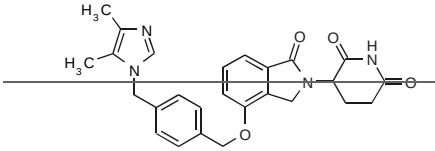


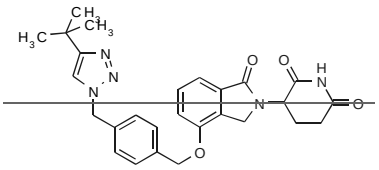
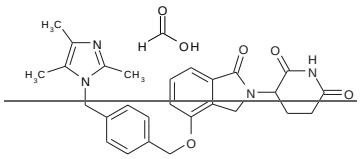
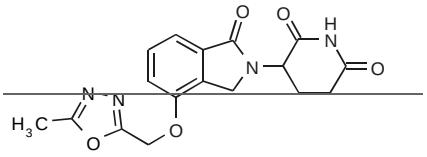
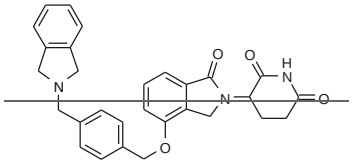
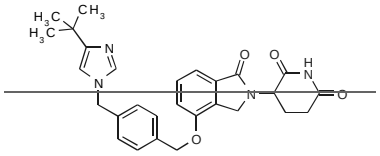
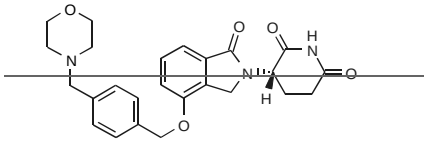
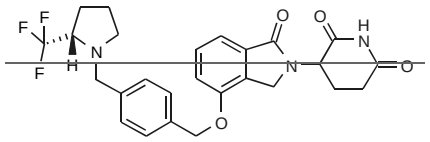
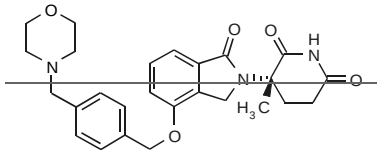
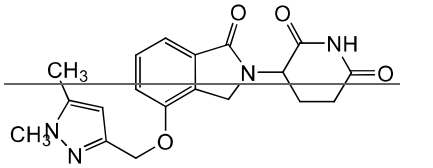
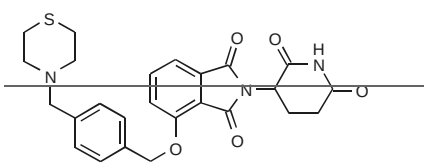
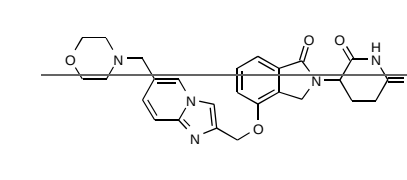
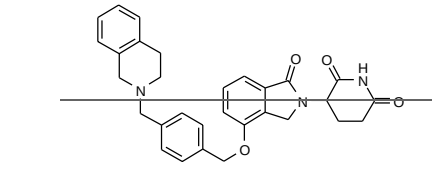
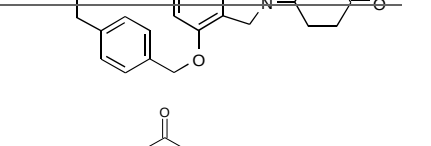
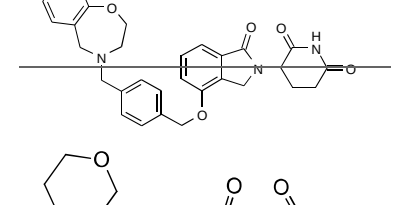
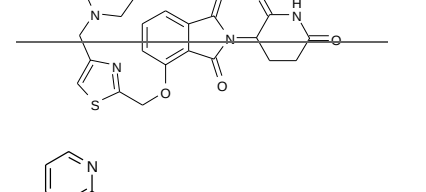
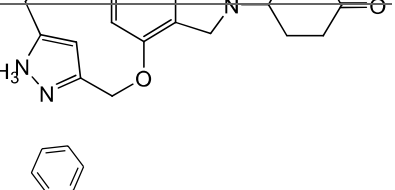
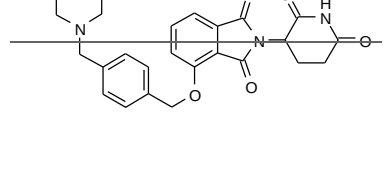
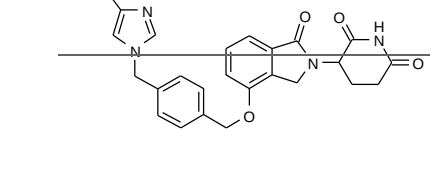


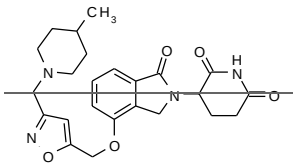
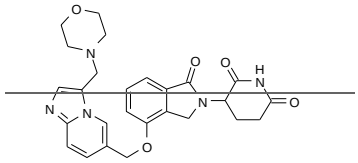
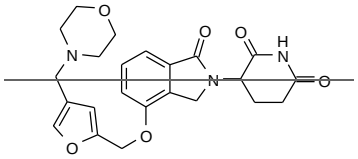
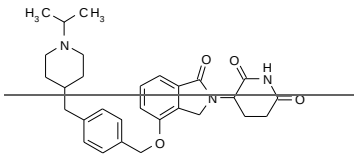
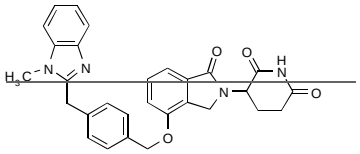
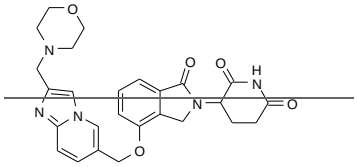
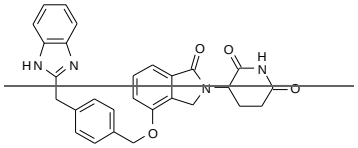
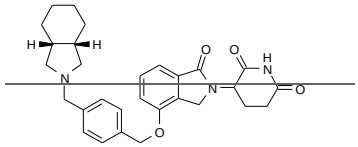
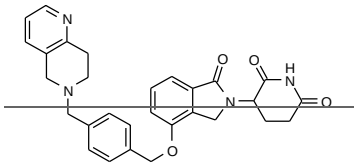
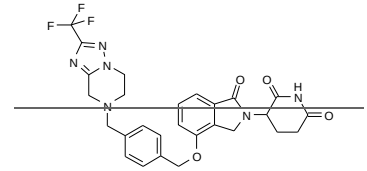
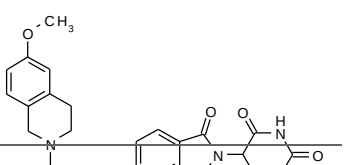
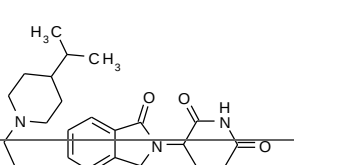
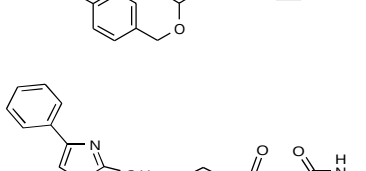
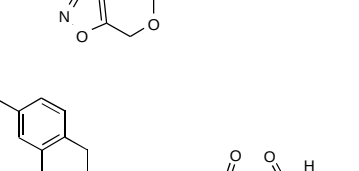
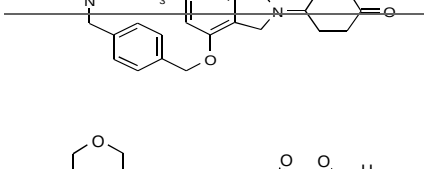
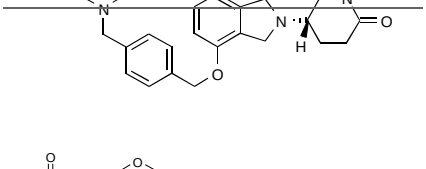
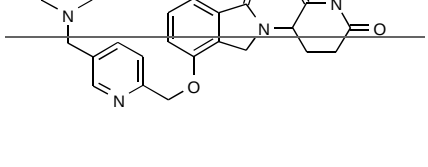
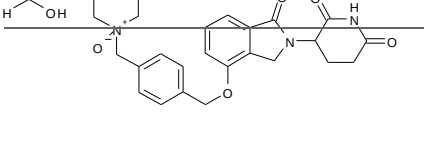


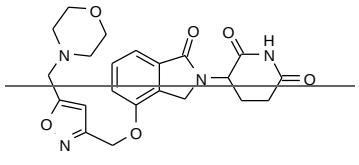


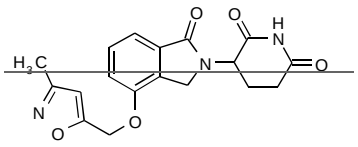


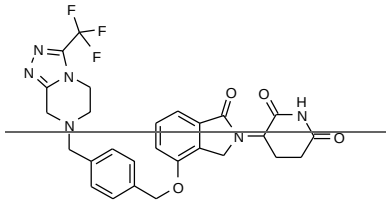


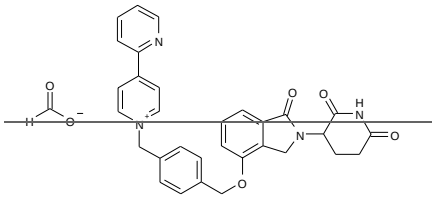



















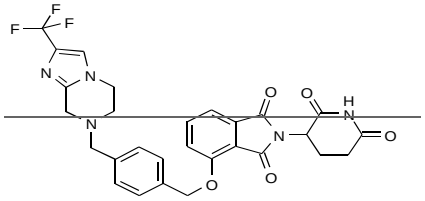



















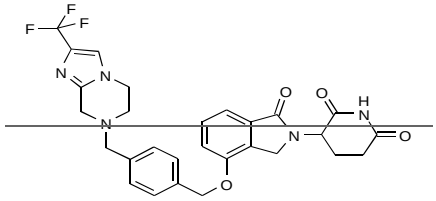


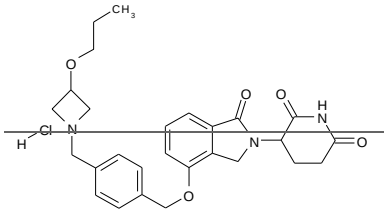


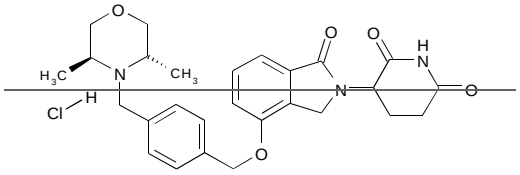


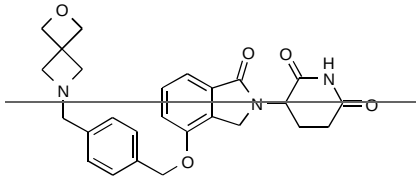


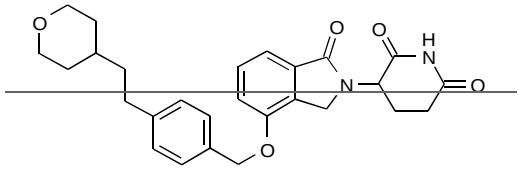


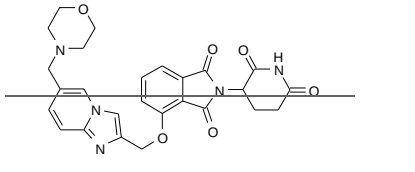


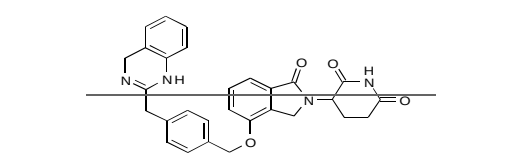


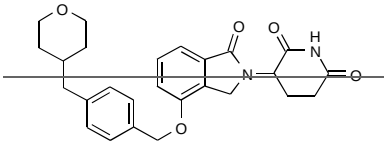


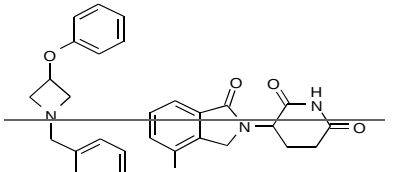


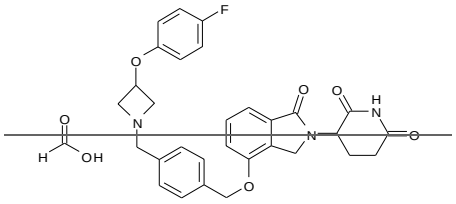


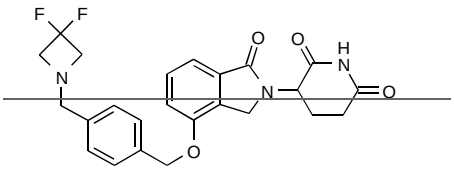


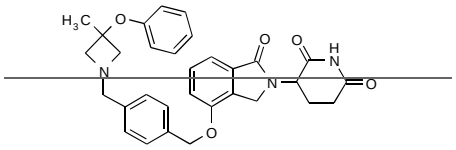


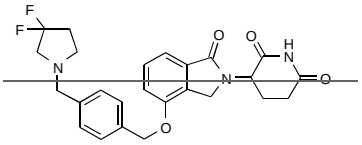


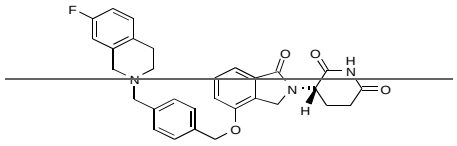


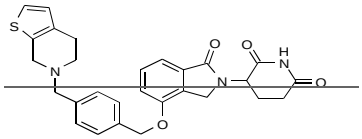


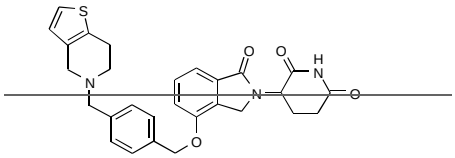


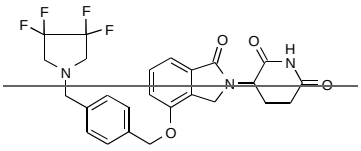


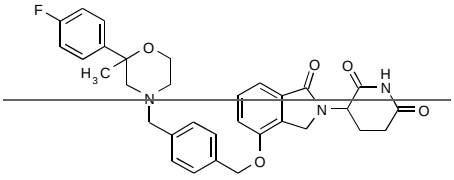


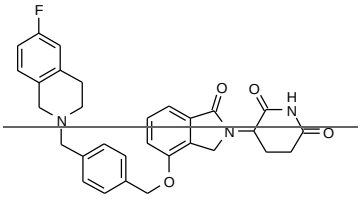


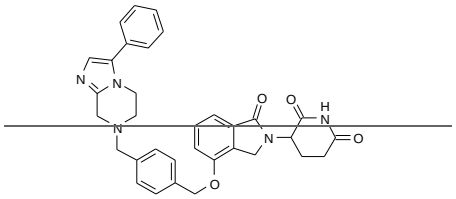


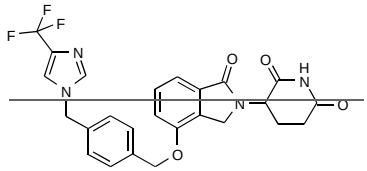


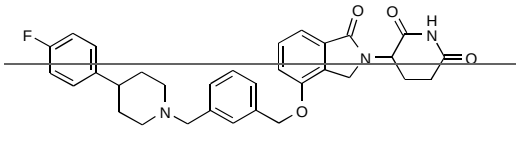


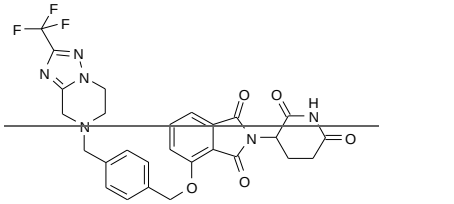


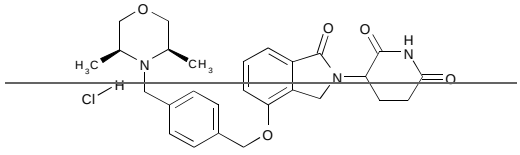


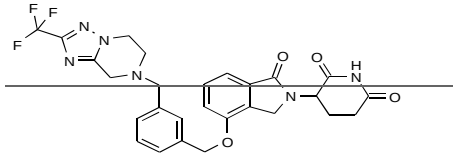


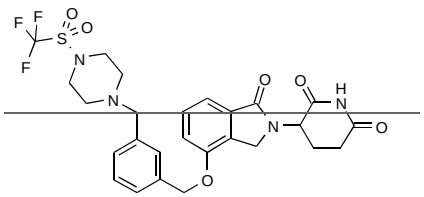


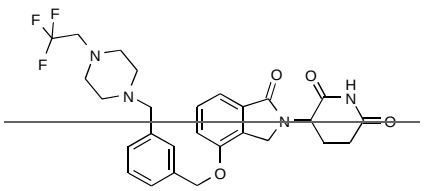


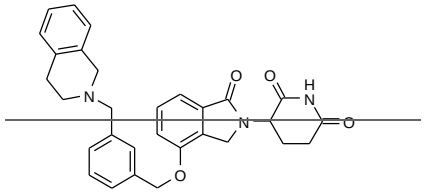


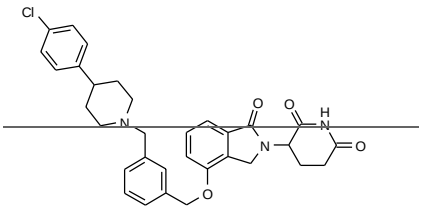


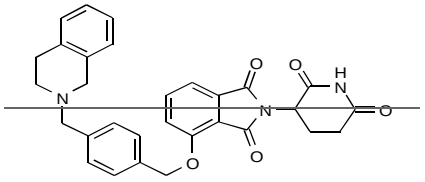


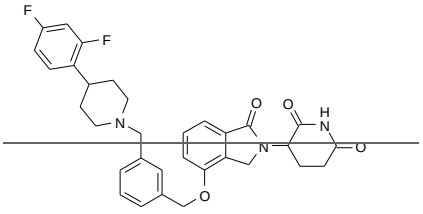


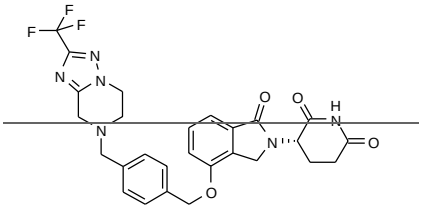


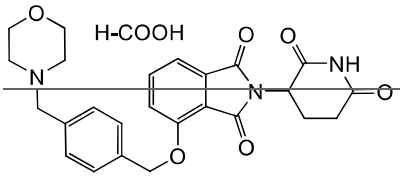


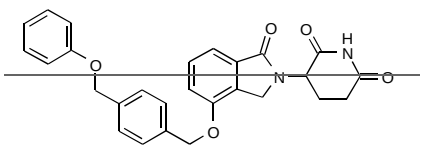


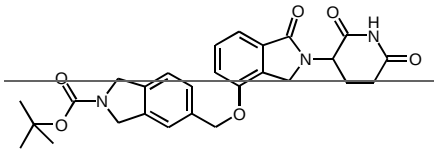


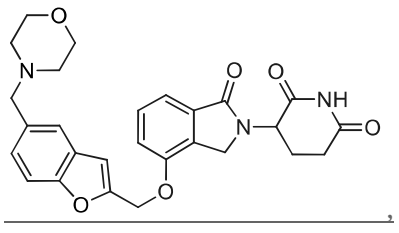


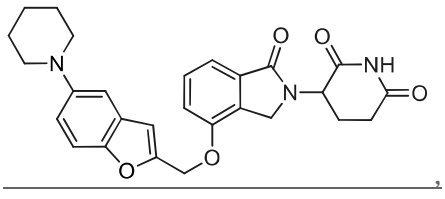


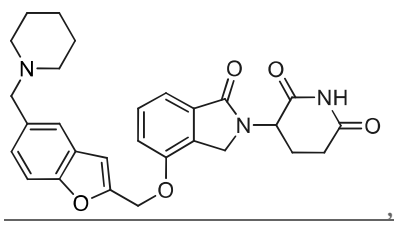


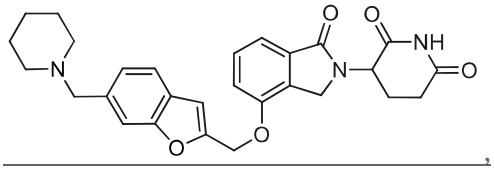


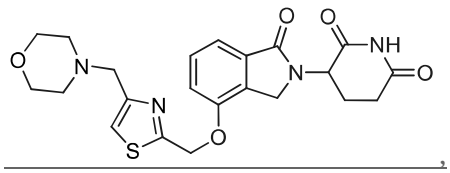


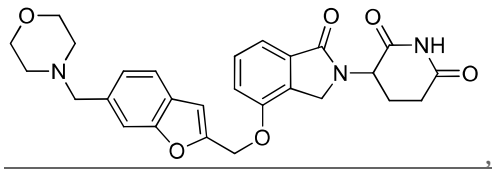


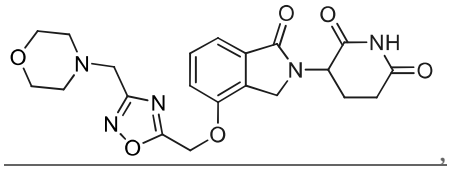


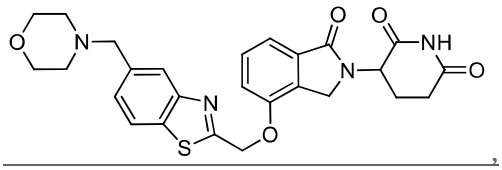


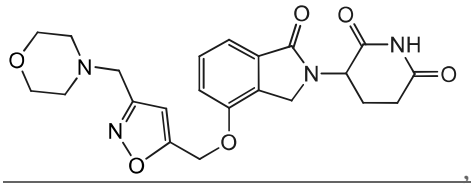


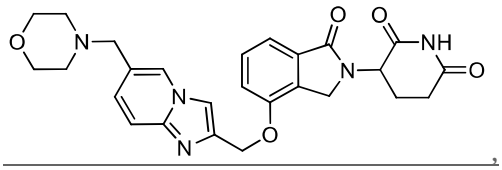


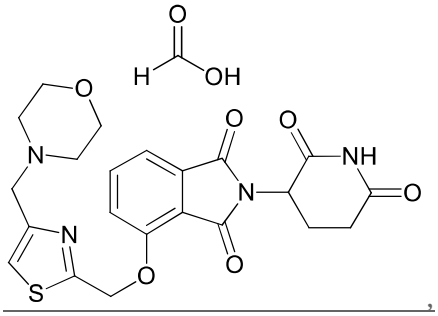


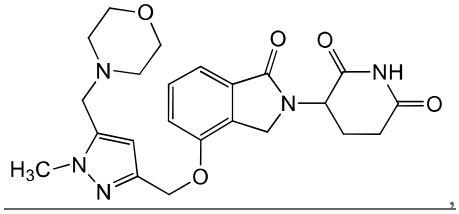


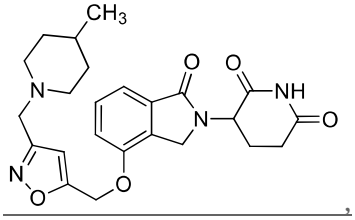


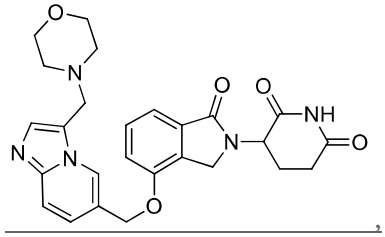


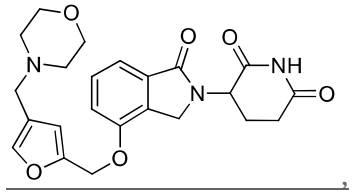


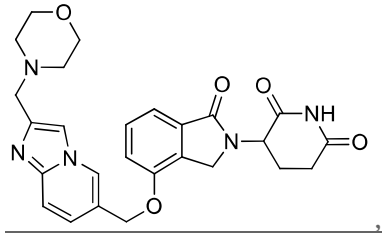


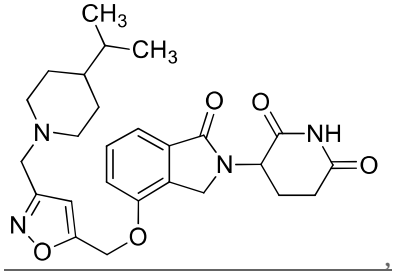


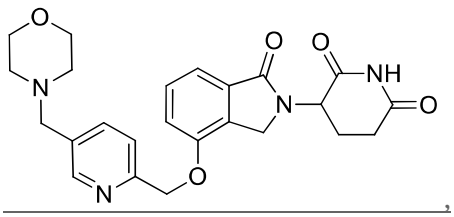


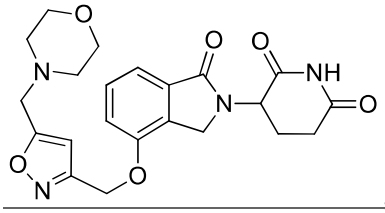




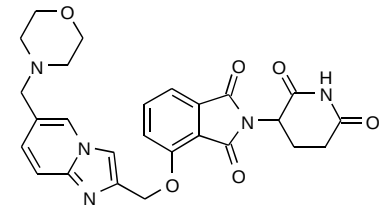








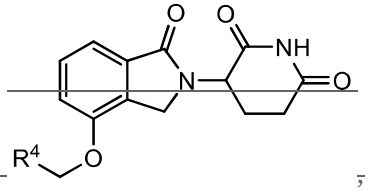
, or



,

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

~~8. A compound of formula (II):~~



~~,~~

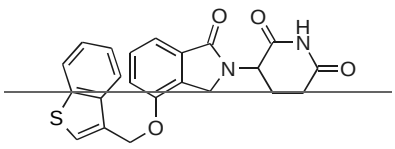
~~(II)~~

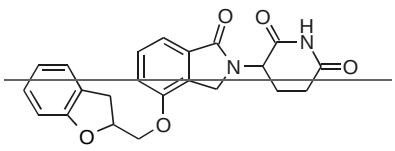
~~or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:~~

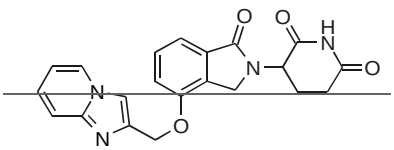
~~R^4 is unsubstituted 9 to 10 membered bicyclic ring is benzothiazole, quinoline, isoquinoline, naphthalene, 2,3-dihydro-1H-indene, benzo[d][1,2,3]triazole, imidazo[1,2-a]pyridine, benzofuran, 2,3-dihydrobenzofuran, benzothiophene, benzo[d]oxazole isoindoline or chroman;~~

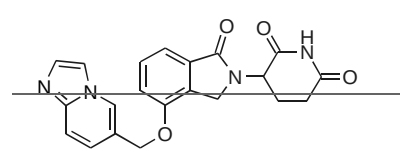
~~with the proviso that if the bicyclic ring is benzofuran or benzothiophene, then the ring is not connected to the isoindole ring through the 2-position.~~

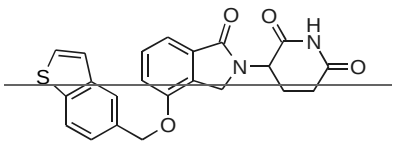
~~9. The compound of claim 8, which is:~~

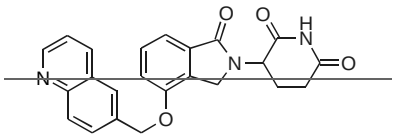


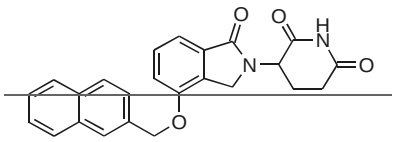


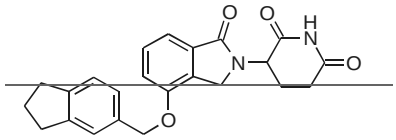


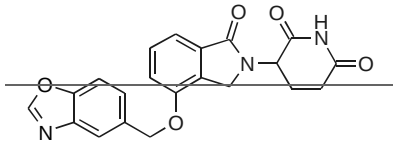


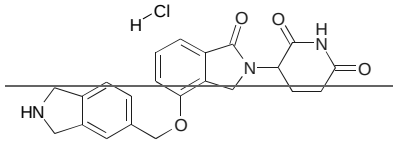


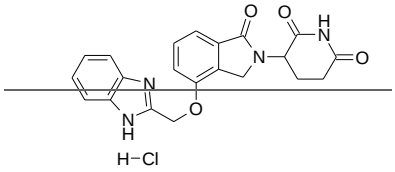








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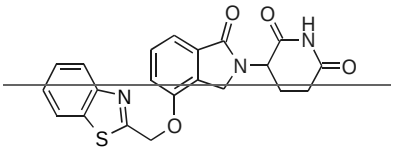
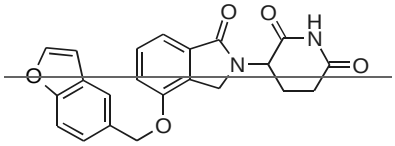
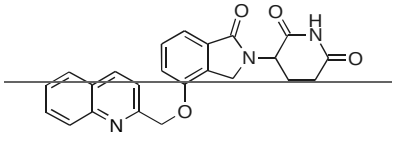
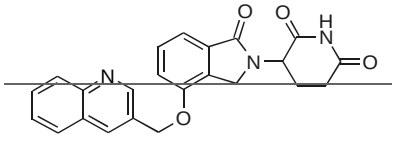
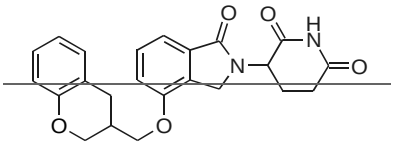
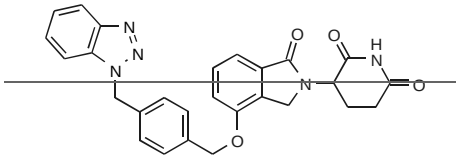






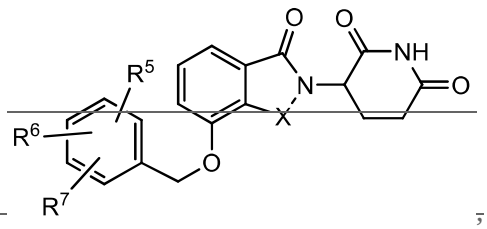






or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

10. A compound of formula (III):



(III)

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

X is CH_2 or C=O;

R^5, R^6 and R^7 are each independently hydrogen, halogen, nitro, carbamoyl, amino, $-SO_2R^8$, $CONR^9R^{10}$, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkoxy, said alkyl or alkoxy may be optionally substituted with one or more halogen, amino, hydroxyl, or NR^9R^{10};

R^8 is: $(C_1$-$C_6)$alkyl, optionally substituted with $(C_1$-$C_6)$alkyl or $(C_6$-$C_{10})$aryl; amino, optionally substituted with $(C_1$-$C_6)$alkyl or $(C_6$-$C_{10})$aryl; or 6 to 10 membered heterocycle, optionally substituted with $(C_1$-$C_6)$alkyl or $(C_6$-$C_{10})$aryl;

R^9 and R^{10} are each independently hydrogen, 6 to 10 membered aryl, COO $(C_1$-$C_6)$alkyl, $(C_0$-$C_6)$alkyl-CHO, $(C_0$-$C_6)$alkyl-COOH, $(C_0$-$C_6)$alkyl-$NR^{9'}R^{10'}$, $(C_0$-$C_6)$alkyl-(5 to 10 membered heterocycle), $(C_1$-$C_6)$alkyl-OH, $(C_1$-$C_6)$alkyl-O-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl, or $(C_3$-$C_6)$cycloalkyl; or

R^9 and R^{10} together may form an optionally substituted 5 to 6 membered ring containing one or more heteroatoms; and

$R^{9'}$ and $R^{10'}$ are each independently hydrogen or $(C_1$-$C_6)$alkyl;

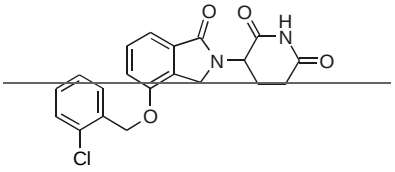
with the proviso that all of R^5-R^7 cannot be hydrogen; and

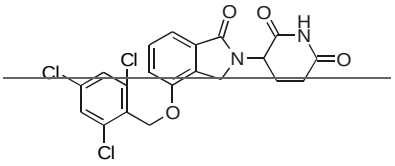
with the proviso that if one of R^5-R^7 is hydrogen and the remaining two of R^5-R^7 are both chloride, then the two chloride atoms cannot be on 3 and 4 position of the phenyl ring.

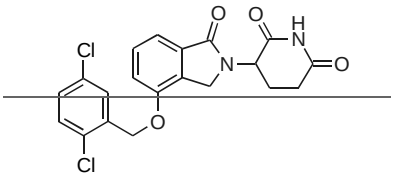
~~11. The compound of claim 10, wherein one of R^5-R^7 is hydrogen, and the remaining two of R^5-R^7 are each independently halogen, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.~~

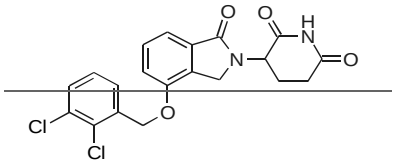
~~12. The compound of claim 10, wherein two of R^5-R^7 are hydrogen and the remaining one of R^5-R^7 is halogen, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.~~

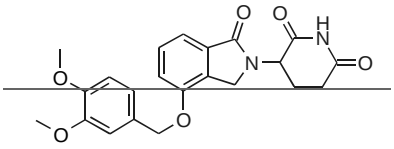
~~13. The compound of claim 10, which is:~~

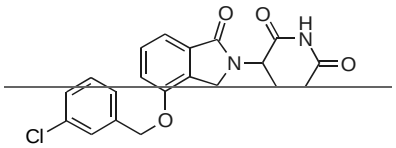


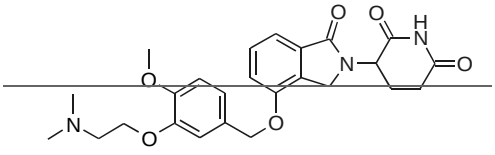


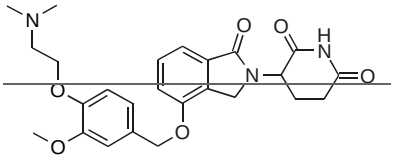


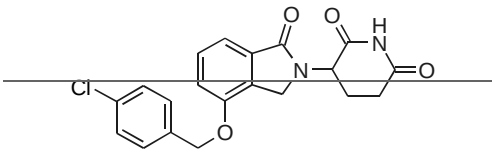


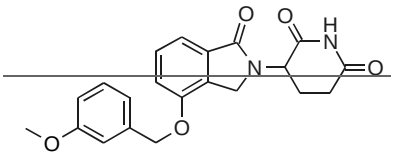


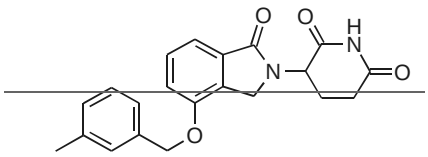


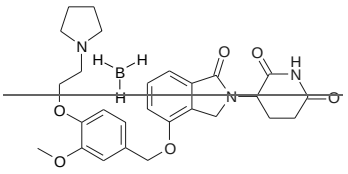


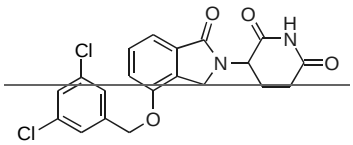


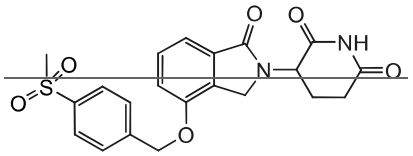


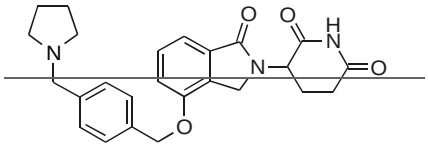


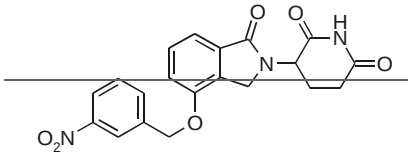


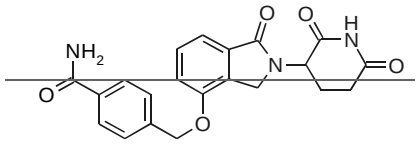


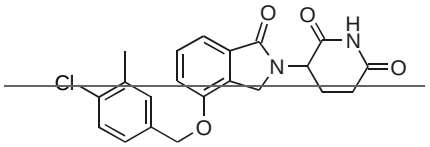


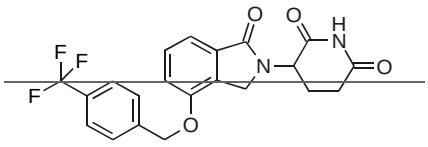


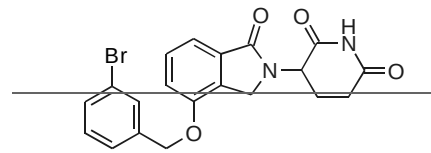


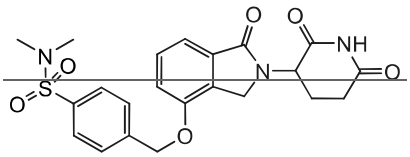


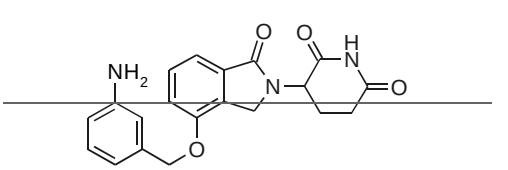


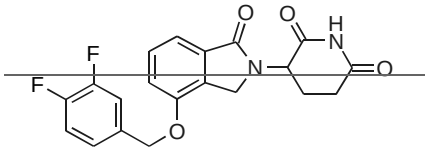


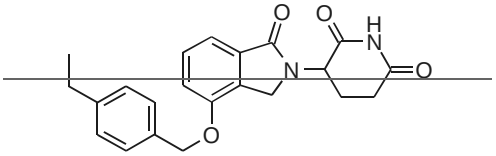


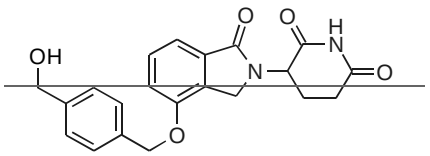


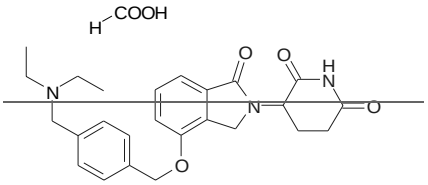


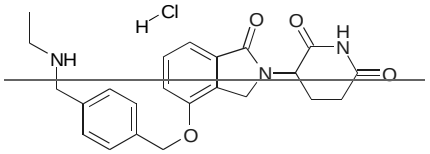


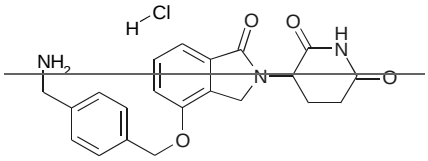


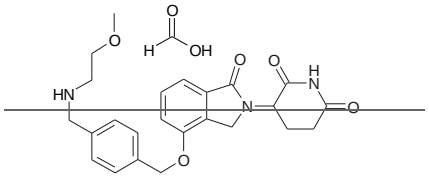


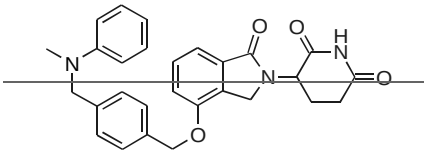


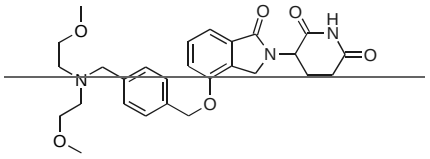


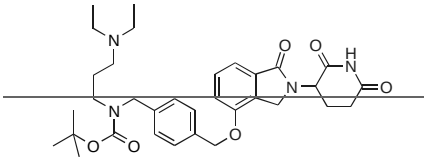


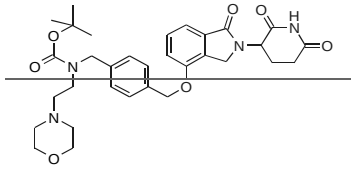


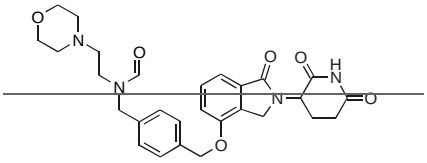


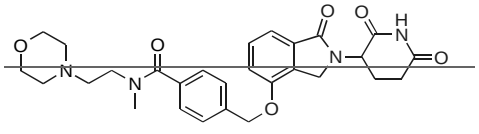


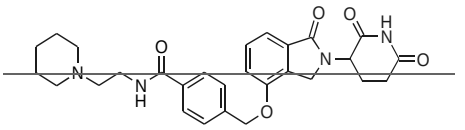


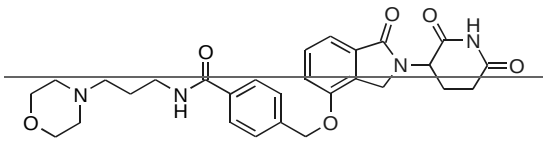


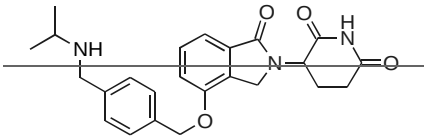


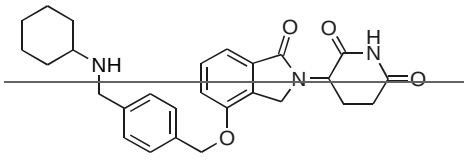


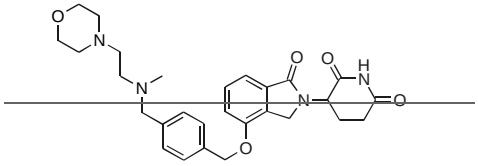


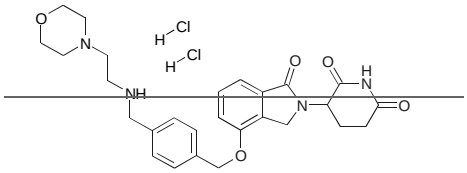


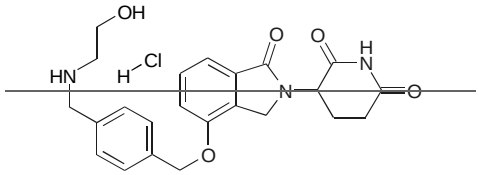


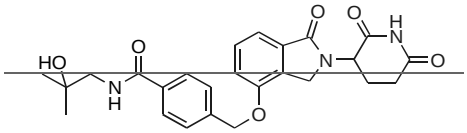


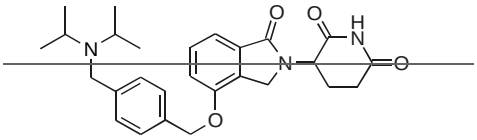


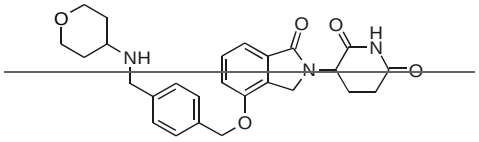


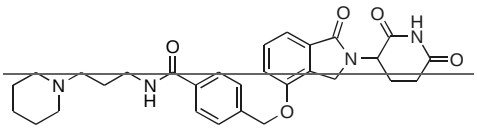


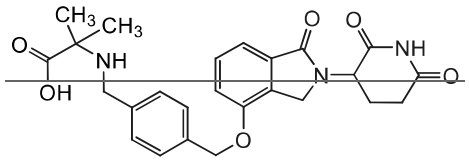


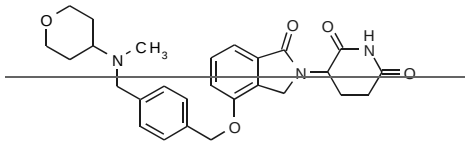


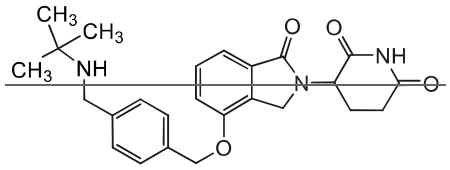


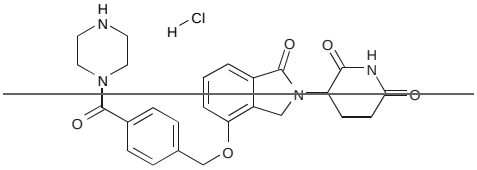


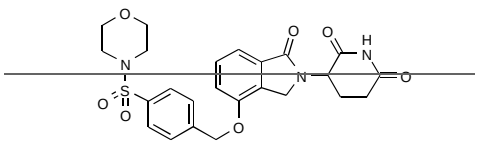


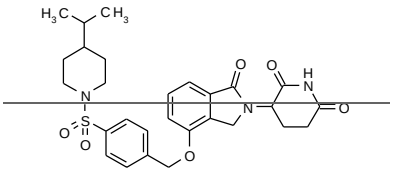


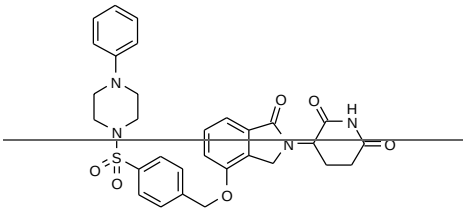


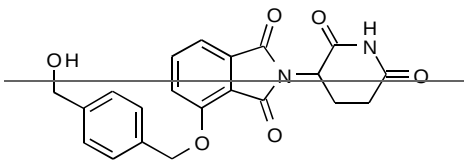


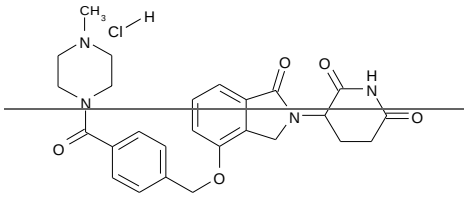






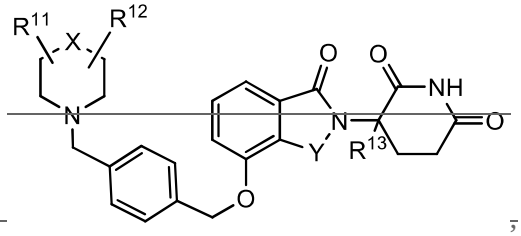






or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

14. A compound of formula (IV):



(IV)

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

X is N or C;

Y is CH_2 or C=O;

R^{11} and R^{12} are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl $(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryl, $CO(C_1$-$C_6)$alkyl, $CO(C_3$-$C_6)$cycloalkyl, $CO(C_6$-$C_{10})$aryl, $COO(C_1$-$C_6)$alkyl, halogen, hydroxyl, oxo, 3 to 10 membered heterocycle, 6 to 10 membered heteroaryl, $NHCO(C_1$-$C_6)$alkyl, $(CH_2)_n$ phenyl, $SO_2(C_1$-$C_6)$alkyl, $SO_2(C_3$-$C_6)$cycloalkyl, $SO_2(C_6$-$C_{10})$aryl or $NR^{14}R^{15}$, wherein the alkyl, aryl or heteroaryl portion of each of the groups may be optionally substituted with one or more halogen, hydroxyl or -$(C_1$-$C_6)$alkoxy;

~~R^{13} is hydrogen or $(C_1$-$C_6)$alkyl;~~

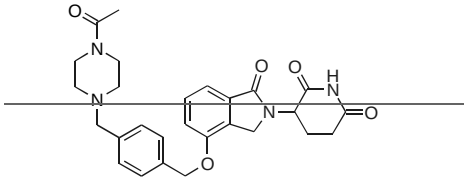
~~R^{14} and R^{15} are each independently hydrogen or $(C_1$-$C_6)$alkyl; and~~

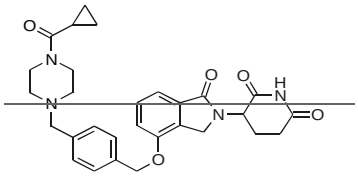
~~n is 0, 1, 2 or 3.~~

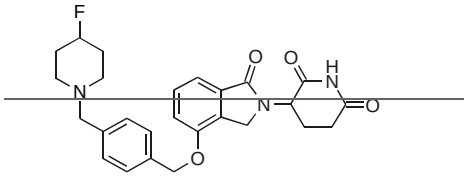
~~15. The compound of claim 14, wherein X is N.~~

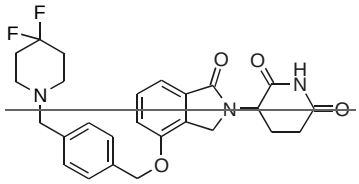
~~16. The compound of claim 14, wherein Y is CH_2.~~

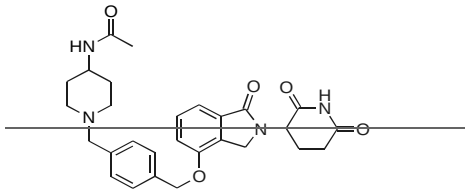
~~17. The compound of claim 14, which is:~~

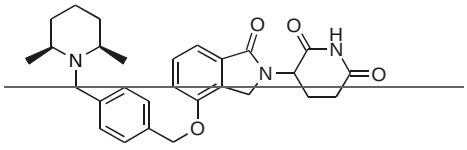


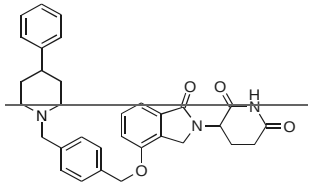


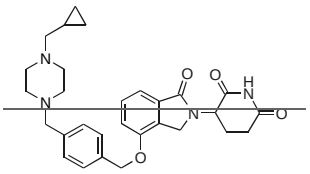


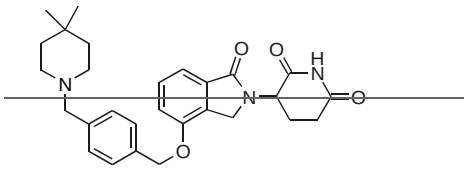


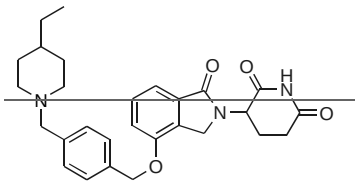


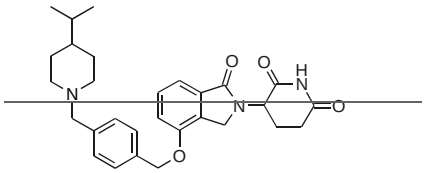


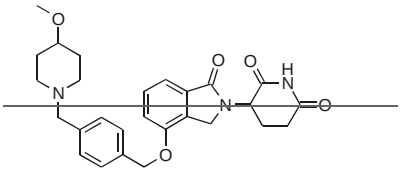


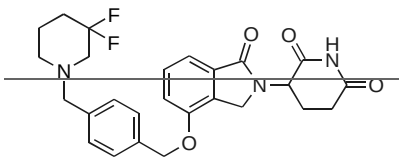


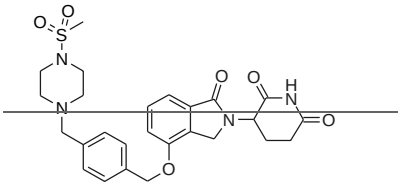


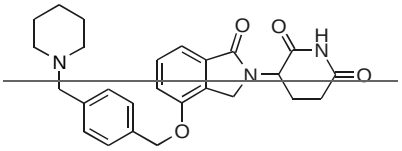


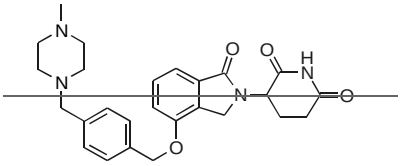


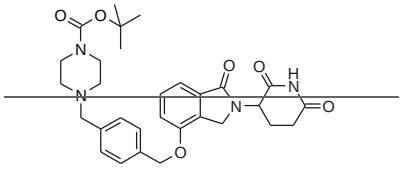


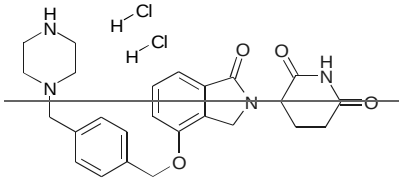


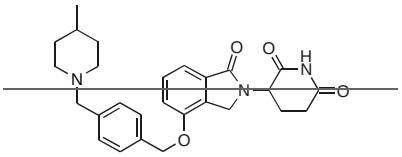


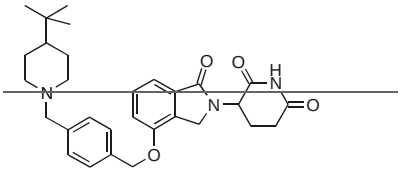


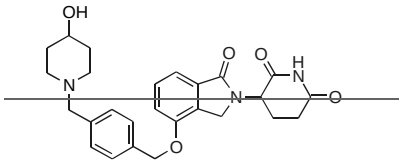


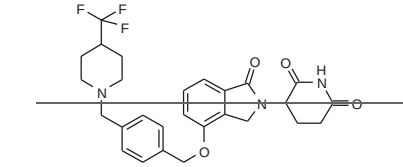


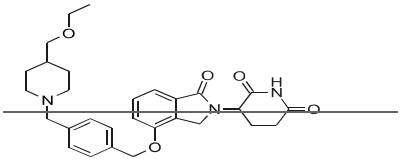


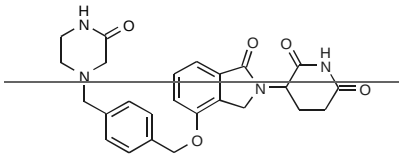


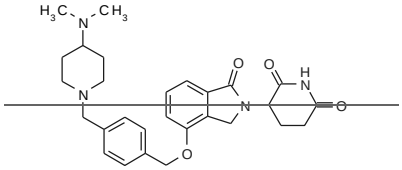


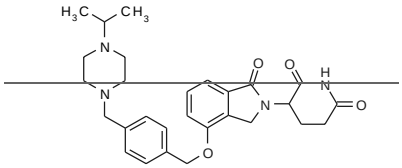


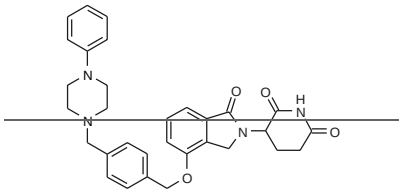


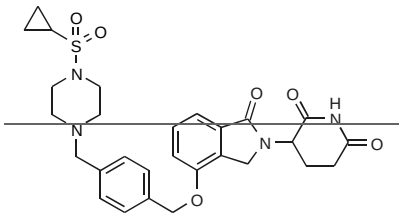


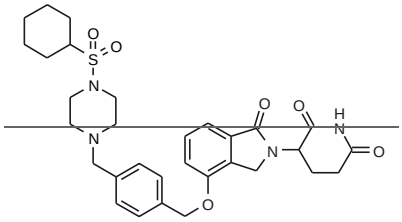


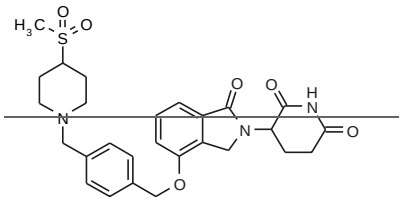


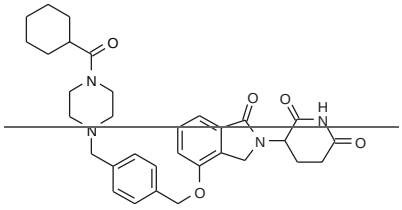


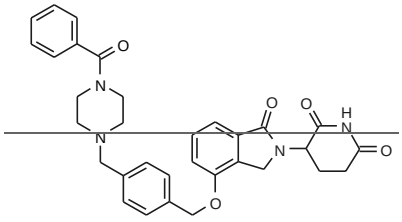


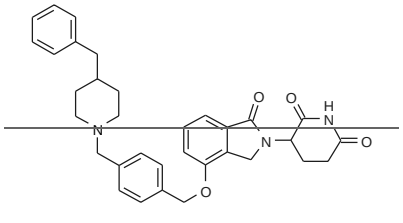


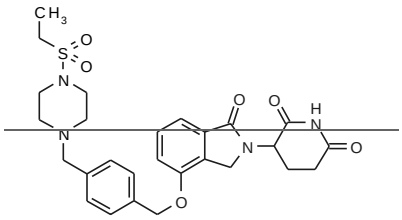


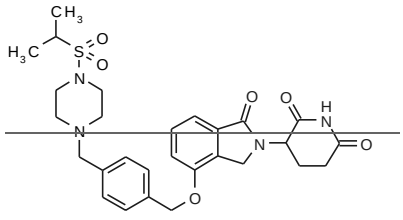


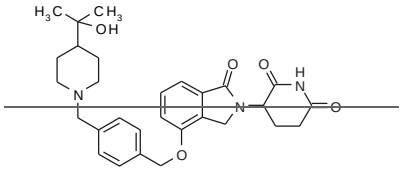


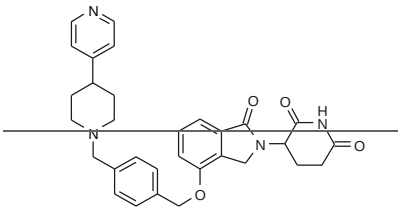


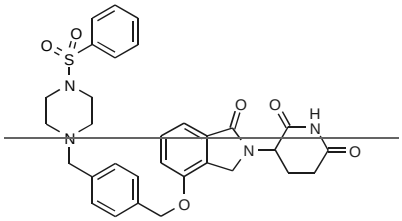


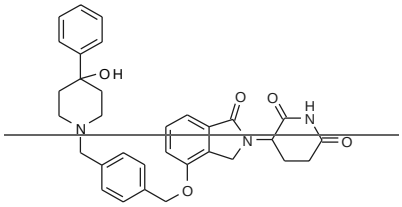


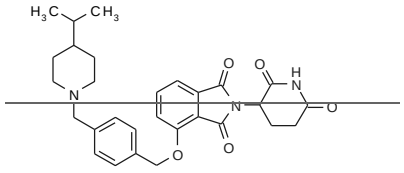


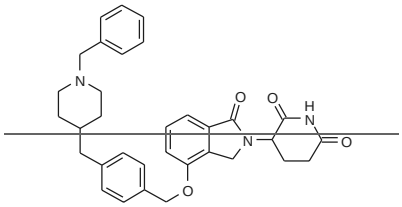


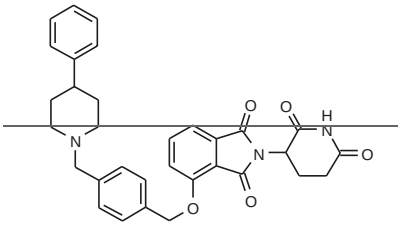


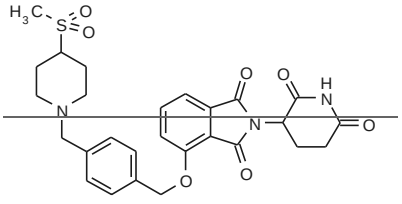


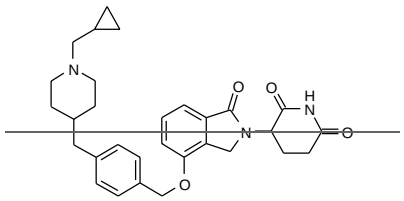


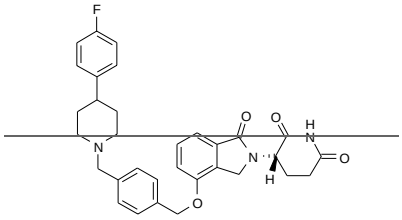


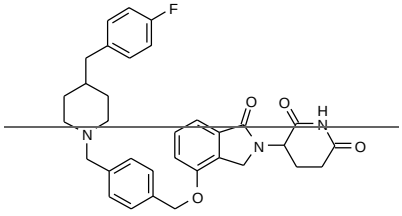


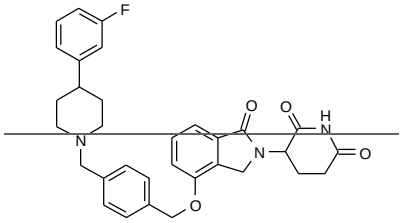


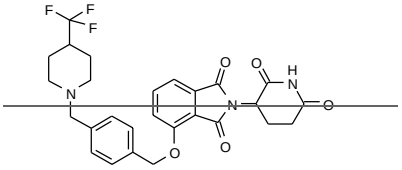


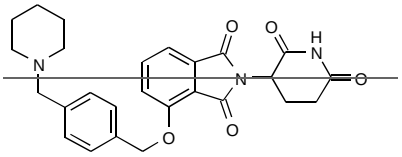


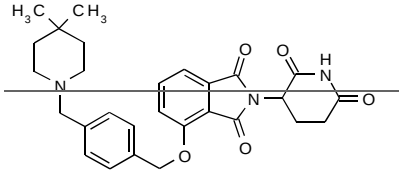


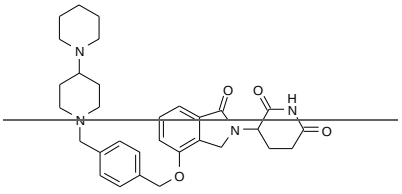


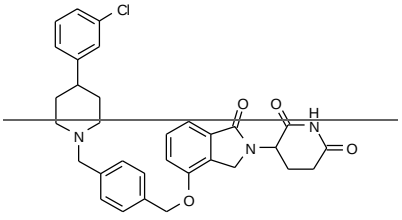


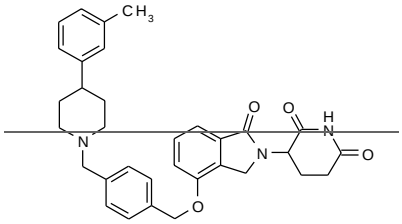


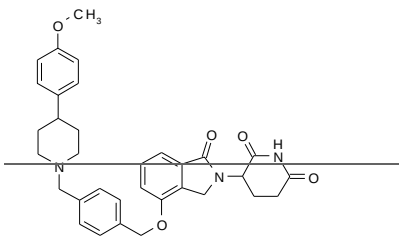


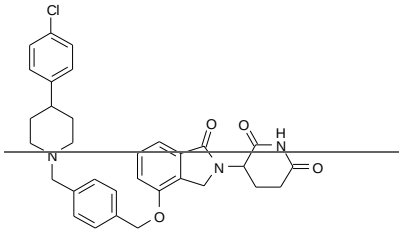


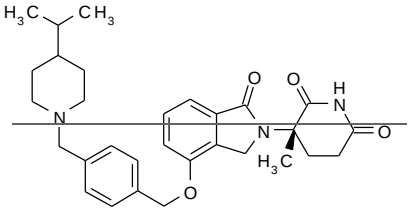


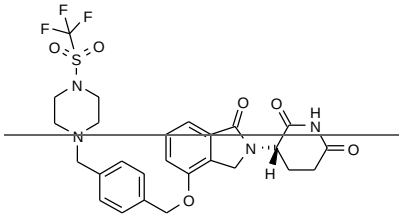


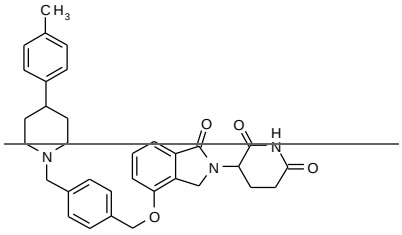


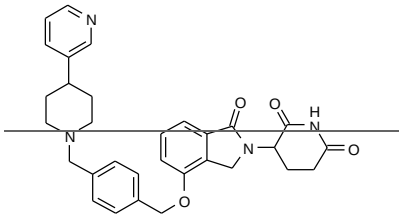


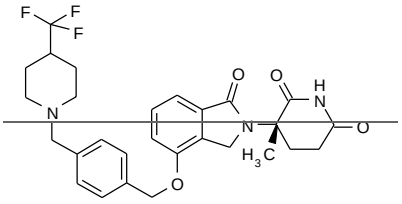


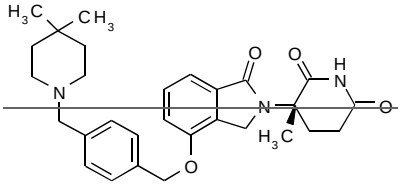


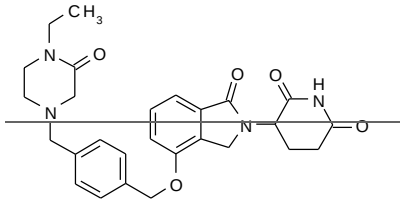


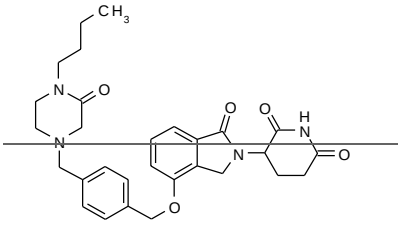


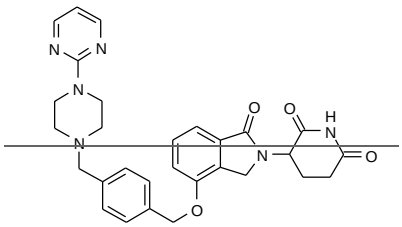


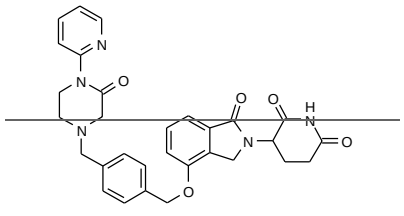


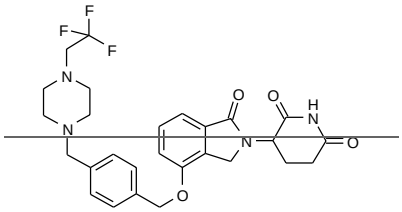


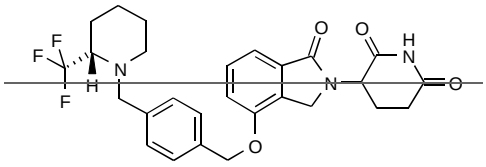


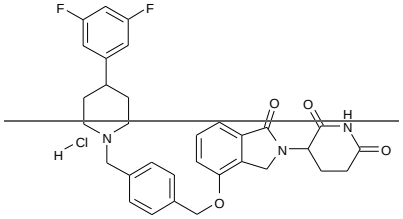


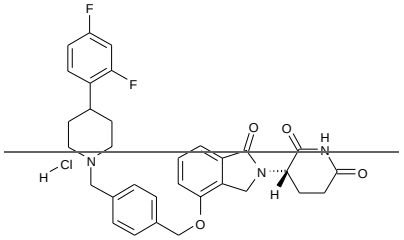


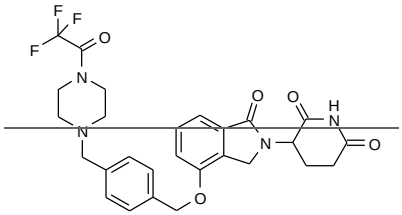


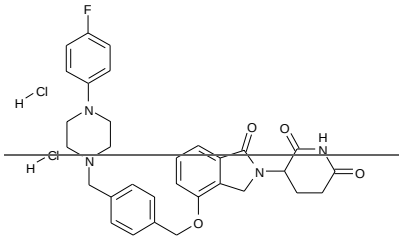


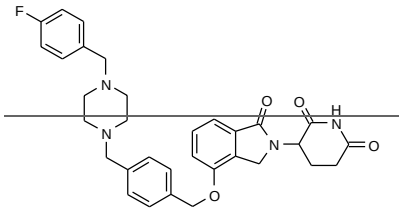


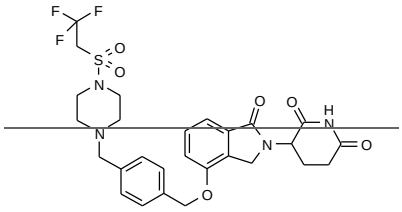


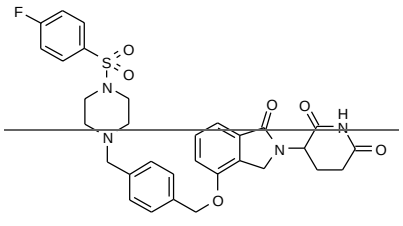


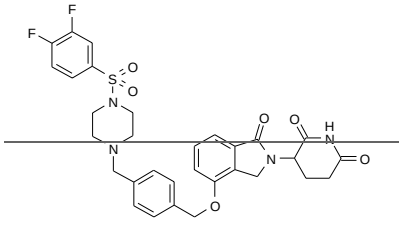


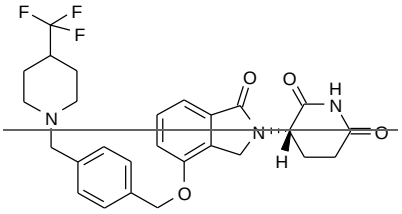


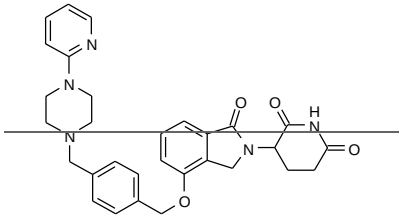


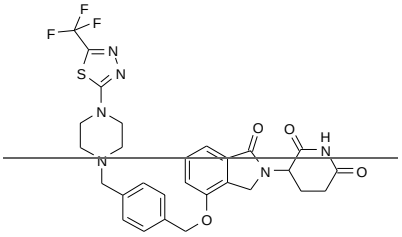


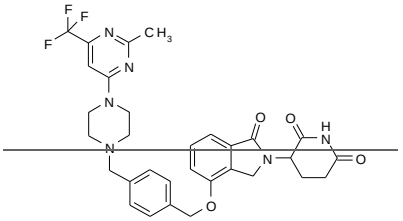


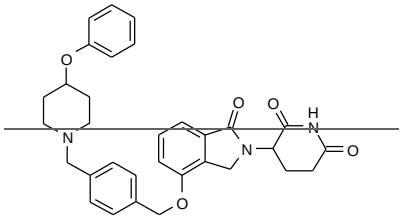


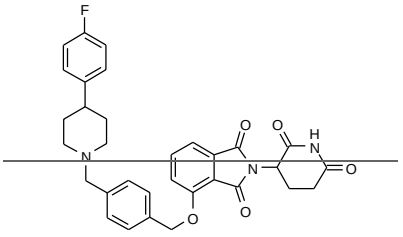


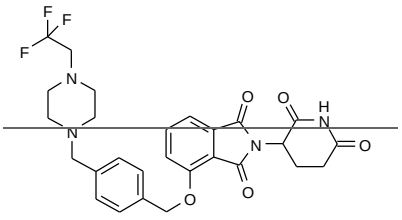


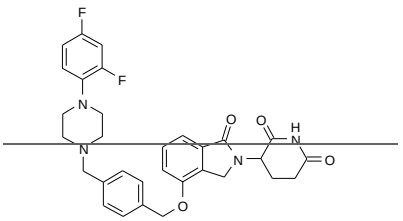


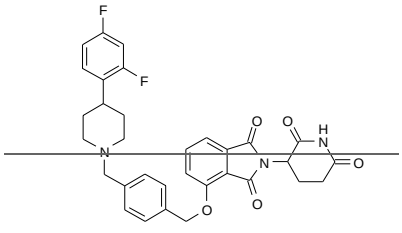
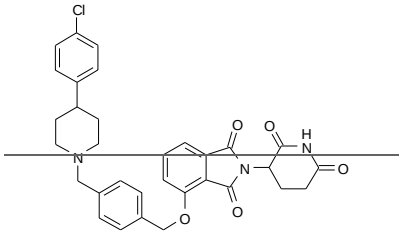
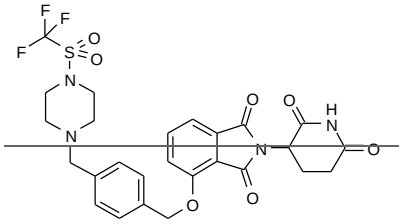
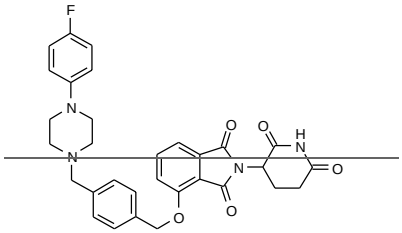






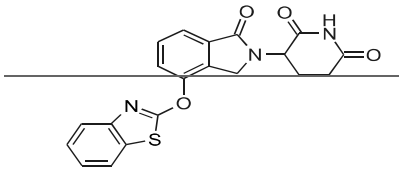
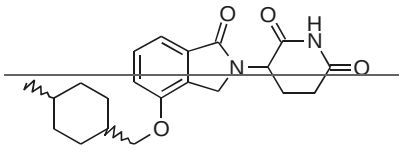
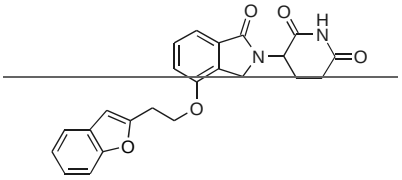
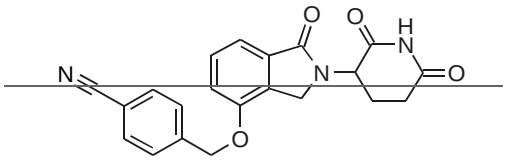
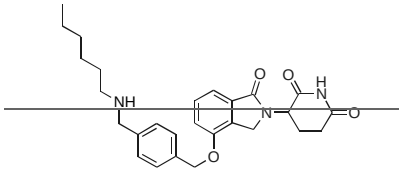
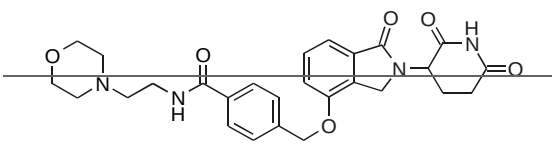


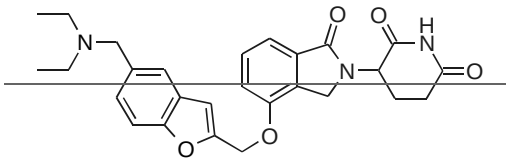


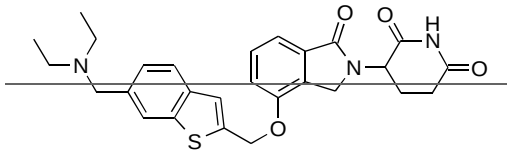





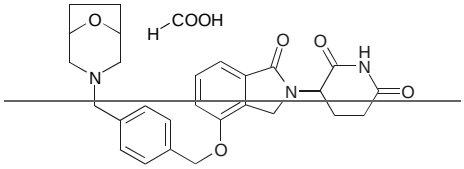
~~or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.~~

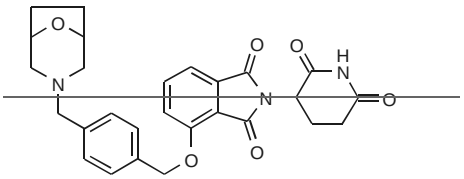
~~18. A compound, which is:~~

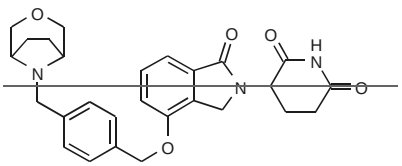







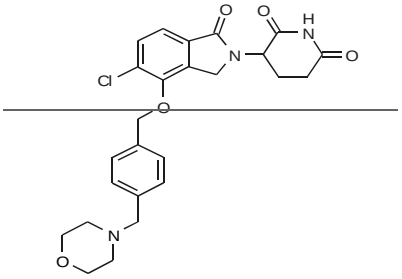


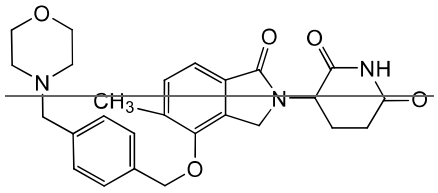


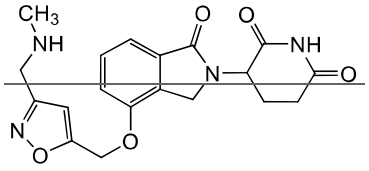


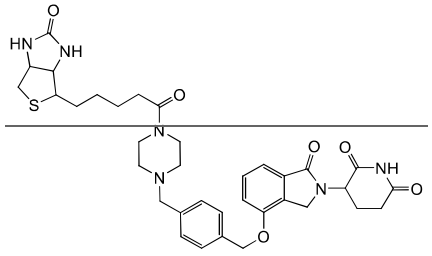


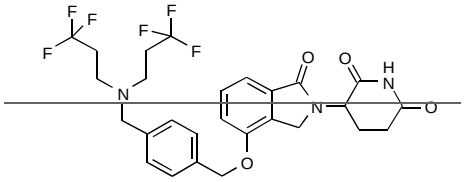


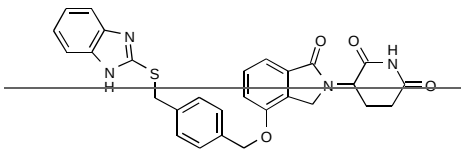


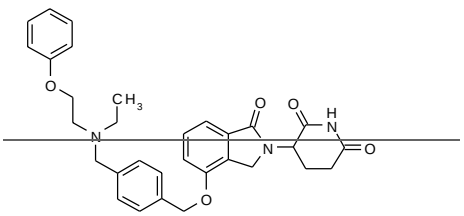


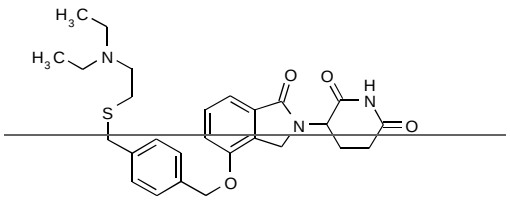












~~or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.~~

8~~19~~. A pharmaceutical composition comprising a compound of any one of claims 1-7~~18~~, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

9~~20~~. Use of a compound of any one of claims 1-7, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition of claim 8, in the manufacture of a medicament for ~~A method of~~ treating, managing or preventing a disease or disorder ~~comprising administering to a patient a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof~~, wherein the disease or disorder is cancer, a disorder associated with angiogenesis, pain, macular degeneration or a related syndrome, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis or a related disorder, dysfunctional sleep or a related disorder, an infectious disease, hemoglobinopathy or a related disorder, or a TNFα related disorder.

10. A compound of any one of claims 1-7, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or the pharmaceutical composition of claim 8 for use in therapy.