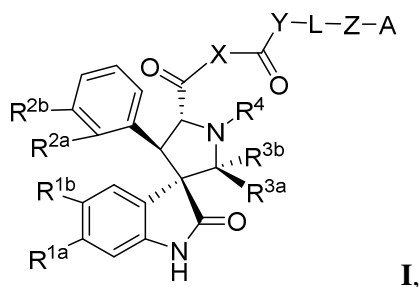


BRIEF SUMMARY

[0010] The present disclosure provides heterobifunctional compounds represented by Formula **I** or Formula **II**, below, and the pharmaceutically acceptable salts and solvates thereof, collectively referred to as "Compounds of the Disclosure." Compounds of the Disclosure are MDM2 protein degraders and thus are useful in treating diseases or conditions wherein inhibition and/or degradation of MDM2 provides a benefit.

[0010a] In one aspect, the present disclosure provides a compound of Formula **I**:



wherein:

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, fluoro, and chloro;

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro;

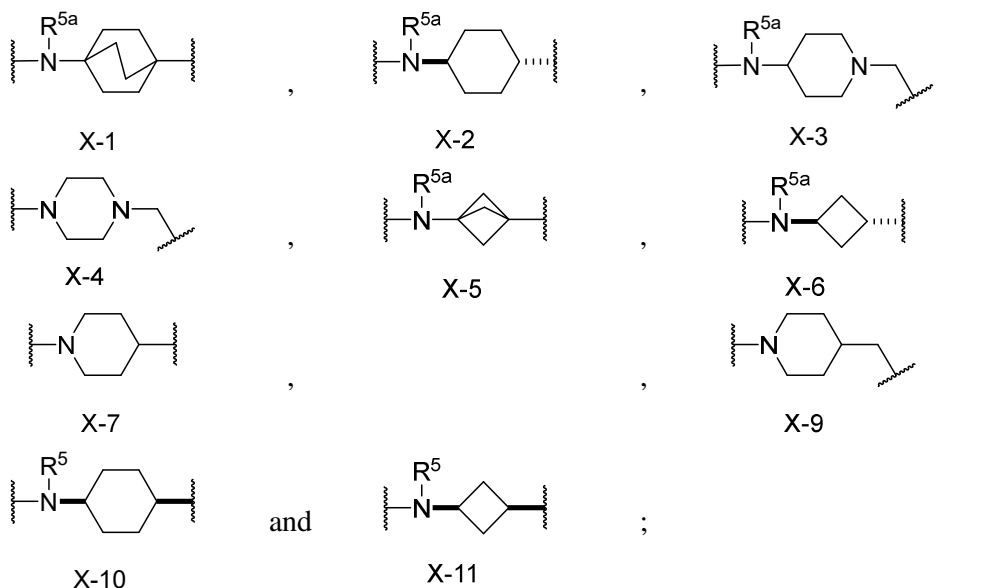
R^{3a} is $-\text{CH}_2\text{C}(\text{CH}_3)_3$;

R^{3b} is hydrogen; or

R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a cyclobutyl, cyclopentyl, or cyclohexyl group that is unsubstituted or substituted with one or two methyl groups;

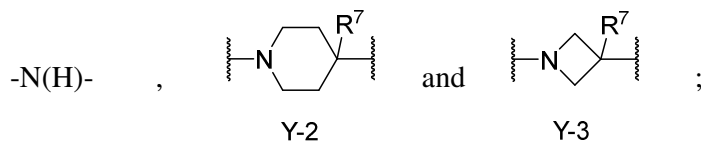
R^4 is selected from the group consisting of hydrogen, methyl, and ethyl;

X is selected from the group consisting of:



wherein the bond projecting to the right is attached to $-\text{C}(=\text{O})-\text{Y}-\text{L}-\text{Z}-\text{A}$;
 each R^5 is independently selected from the group consisting of hydrogen and methyl;

Y is selected from the group consisting of:



wherein the bond projecting to the right is attached to $-\text{L}-\text{Z}-\text{A}$;

R^7 is selected from the group consisting of hydrogen, hydroxy, and methyl;

L is selected from the group consisting of $-(\text{CH}_2)_m-$ and $-(\text{CH}_2\text{CH}_2\text{O})_n-$

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

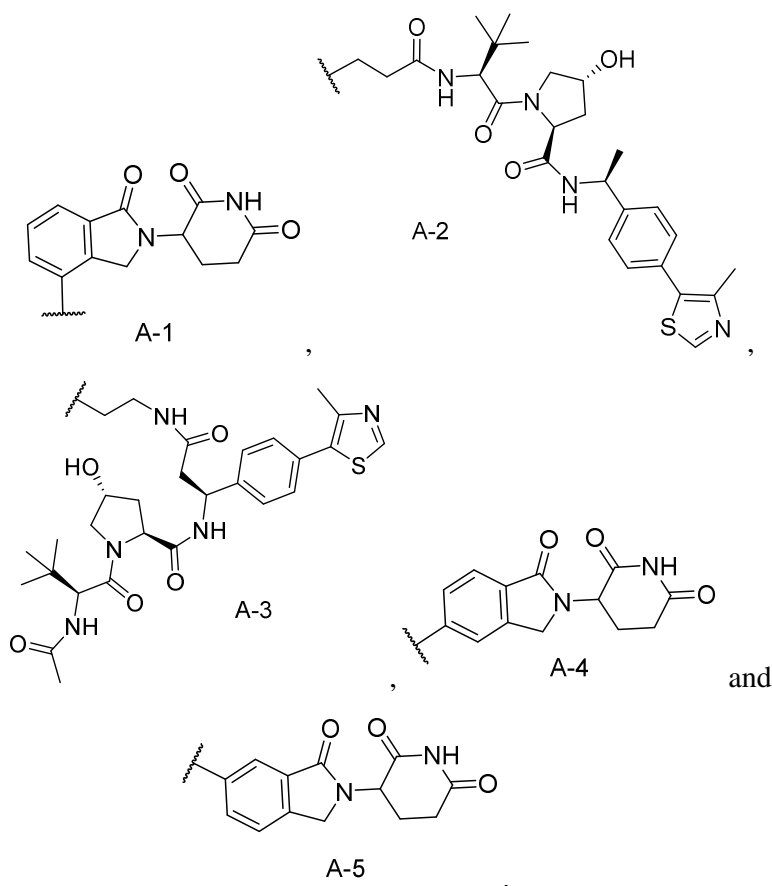
n is 2, 3, 4, 5, or 6;

Z is selected from the group consisting of $-\text{C}\equiv\text{C}-$, $-\text{NH}-$, $-\text{O}-$, and

or

Z is absent;

A is selected from the group consisting of



or a pharmaceutically acceptable salt or solvate thereof.

[0010b] In another aspect, the present disclosure provides a compound that is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)-N-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)acetamide, or a pharmaceutically acceptable salt or solvate thereof.

[0010c] In another aspect, the present disclosure provides a compound that is (2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-N-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)ethynyl)piperidine-1-carbonyl)bicyclo[2.2.2]octan-1-yl)-5-neopentylpyrrolidine-2-carboxamide, or a pharmaceutically acceptable salt or solvate thereof.

[0010d] In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

- [0011]** The present disclosure provides methods of treating a condition or disease by administering a therapeutically effective amount of a Compound of the Disclosure to a subject, e.g., a human, in need thereof. The disease or condition of interest is treatable by degradation of MDM2 proteins, for example, a cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection. Also provided are methods of preventing the proliferation of unwanted proliferating cells, such as in cancer, in a subject comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject at risk of developing a condition characterized by unwanted proliferating cells. In some embodiments, the Compounds of the Disclosure reduce the proliferation of unwanted cells by inducing apoptosis in those cells.
- [0011a]** In another aspect, the present disclosure provides a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in treatment of cancer.
- [0011b]** In another aspect, the present disclosure provides use of a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treatment of cancer.
- [0012]** The present disclosure provides a method of degrading MDM2 proteins in a subject, comprising administering to the subject an effective amount of at least one Compound of the Disclosure.
- [0013]** The present disclosure provides a method of reducing MDM2 protein within a cell of a subject, e.g., a human patient in need thereof, the method comprising administering a Compound of the Disclosure to the subject.
- [0014]** The present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier.
- [0015]** The present disclosure provides a composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier for use treating diseases or conditions wherein degradation of MDM2 proteins provides a benefit, e.g., cancer.

[0016] The present disclosure provides a composition comprising: (a) a Compound of the Disclosure; (b) a second therapeutically active agent; and (c) optionally an excipient and/or pharmaceutically acceptable carrier.

[0017] The present disclosure provides a Compound of the Disclosure for use in treatment of a disease or condition of interest, e.g., cancer.

[0018] The present disclosure provides a use of a Compound of the Disclosure for the manufacture of a medicament for treating a disease or condition of interest, e.g., cancer.

[0019] The present disclosure provides a kit comprising a Compound of the Disclosure, and, optionally, a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and a package insert containing directions for use in the treatment of a disease or condition, e.g., cancer.

[0019a] In another aspect, the present disclosure provides a kit comprising the compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or solvate thereof, to a subject having cancer.

[0020] The present disclosure provides a method of treating a subject having a hematological cancer, the method comprising:

[0021] (a) determining whether an overexpression of MDM2 is present or absent in a biological sample taken from the subject; and

[0022] (b) administering a therapeutically effective amount of a compound of a Compound of the Disclosure to the subject if an overexpression of MDM2 is present in the biological sample.

[0022a] In another aspect, the present disclosure provides use of a compound as described herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a subject having cancer, wherein:

(a) whether an overexpression of MDM2 is present or absent in a biological sample taken from the subject is to be determined; and

(b) a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof, is to be administered to the subject if an overexpression of MDM2 is present in the biological sample.

[0022b] In another aspect, the present disclosure provides use of a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a subject having cancer, wherein the cancer is characterized as having an overexpression of MDM2.

[0022c] In another aspect, the present disclosure provides a compound that is 3-(4-((1-((1r,4r)-4-aminocyclohexane-1-carbonyl)piperidin-4-yl)ethynyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione.

[0023] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

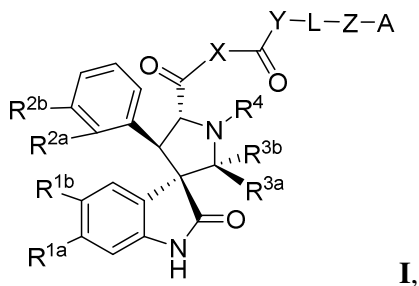
[0024] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the disclosure as claimed.

DETAILED DESCRIPTION OF DRAWINGS

[0025] Fig. 1 is a line graph showing *in vivo* antitumor activity of Cpd. No. 4 and Cpd. No. 6 in the LNCaP prostate cancer xenograft model in SCID mice. Drug was administered I.V., once per week at 50 mg/kg for 5 weeks. Each group had seven mice with each mouse bearing one tumor.

What is claimed is:

1. A compound of Formula I:



wherein:

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, fluoro, and chloro;

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro;

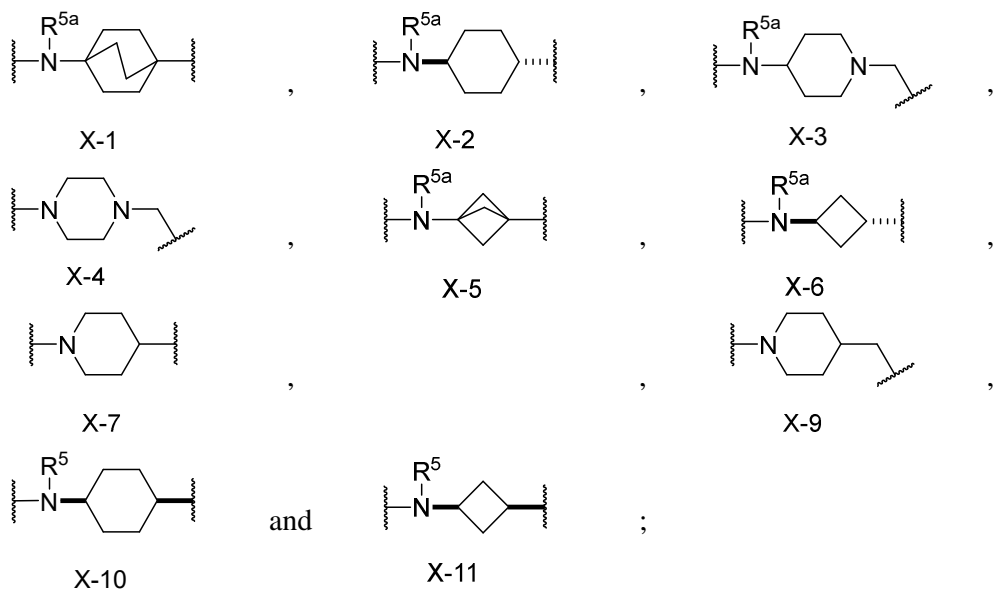
R^{3a} is $-\text{CH}_2\text{C}(\text{CH}_3)_3$;

R^{3b} is hydrogen; or

R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a cyclobutyl, cyclopentyl, or cyclohexyl group that is unsubstituted or substituted with one or two methyl groups;

R^4 is selected from the group consisting of hydrogen, methyl, and ethyl;

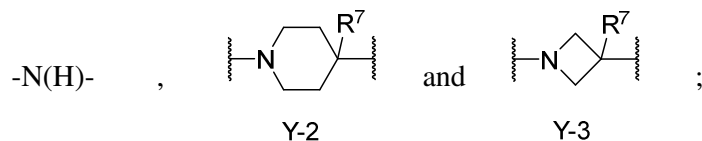
X is selected from the group consisting of:



wherein the bond projecting to the right is attached to $-\text{C}(=\text{O})-\text{Y}-\text{L}-\text{Z}-\text{A}$;

each R⁵ is independently selected from the group consisting of hydrogen and methyl;

Y is selected from the group consisting of:



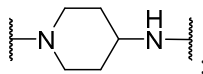
wherein the bond projecting to the right is attached to -L-Z-A;

R⁷ is selected from the group consisting of hydrogen, hydroxy, and methyl;

L is selected from the group consisting of -(CH₂)_m- and -(CH₂CH₂O)_n-

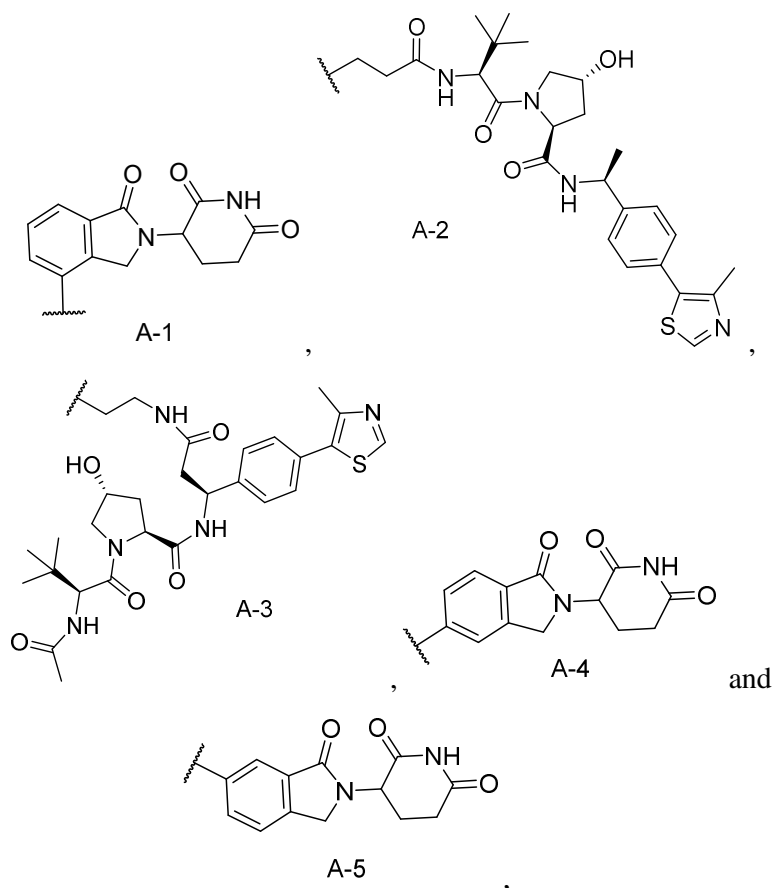
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

n is 2, 3, 4, 5, or 6;

Z is selected from the group consisting of -C≡C-, -NH-, -O-, and ; or

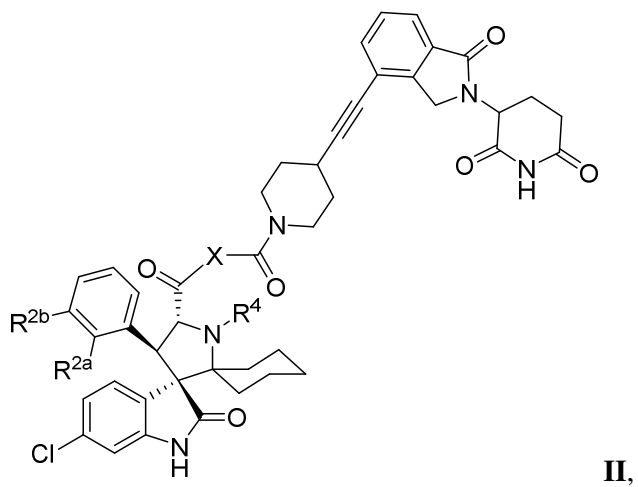
Z is absent;

A is selected from the group consisting of



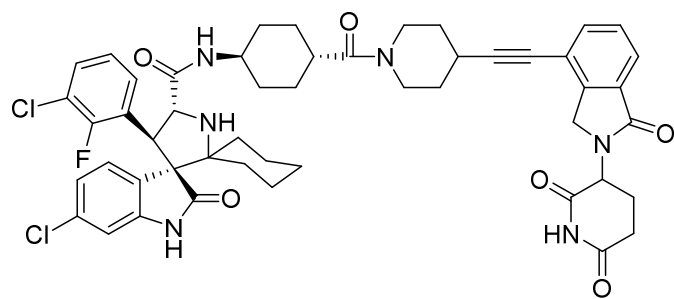
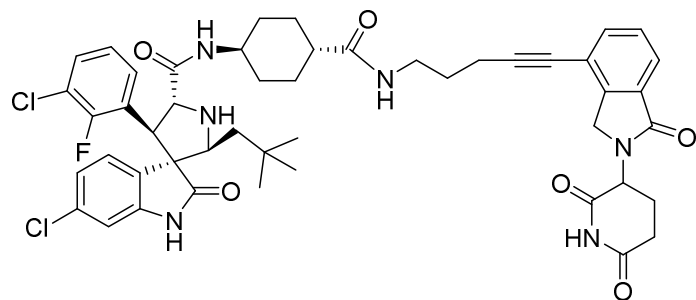
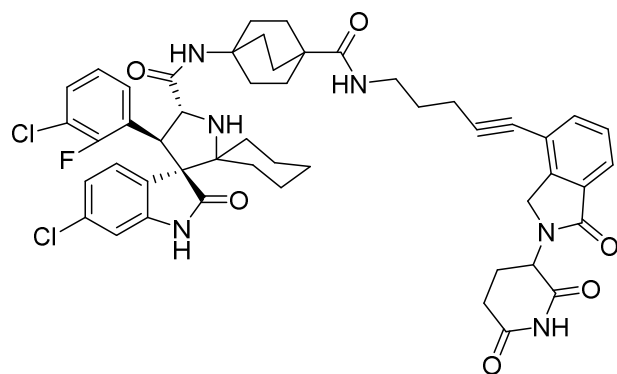
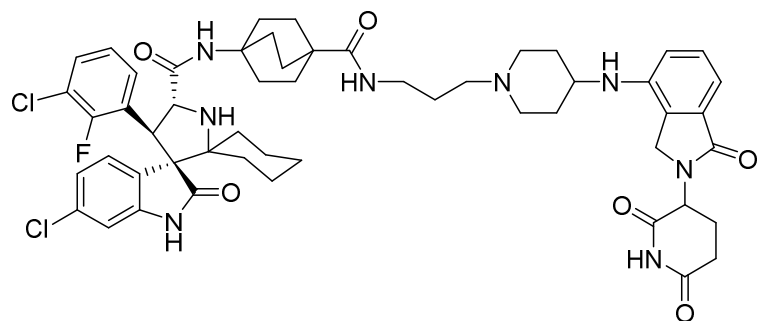
or a pharmaceutically acceptable salt or solvate thereof.

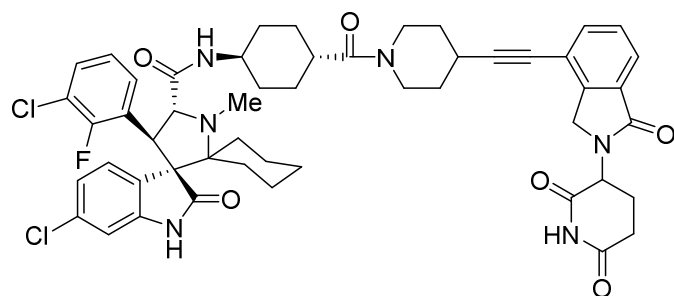
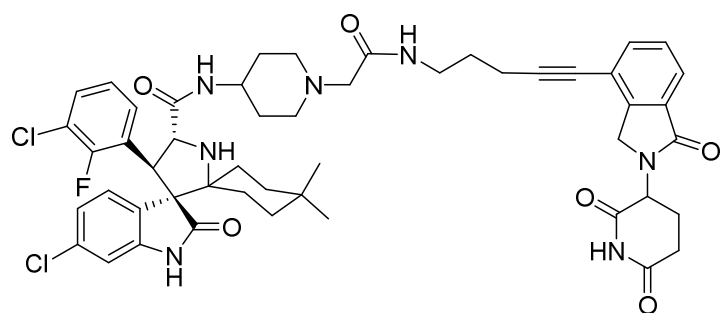
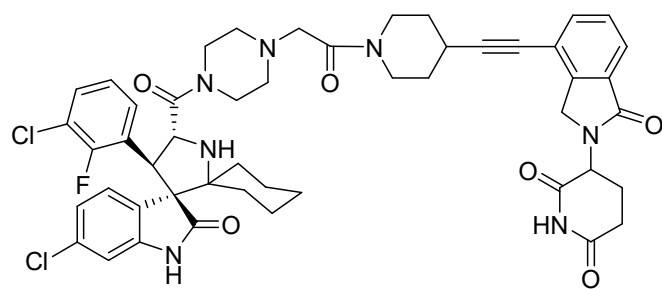
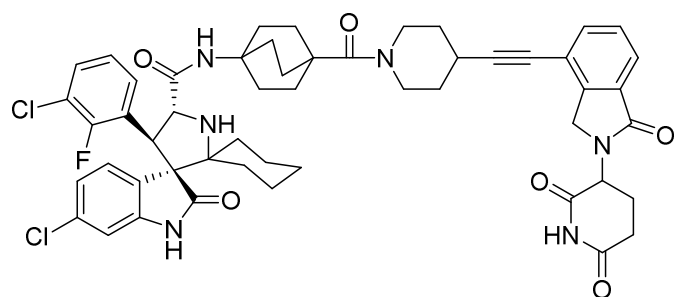
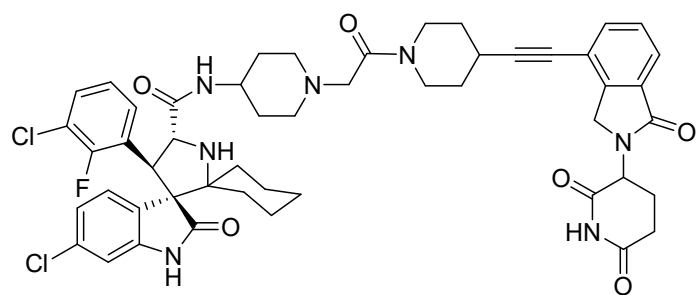
2. The compound of claim 1 of Formula **II**:

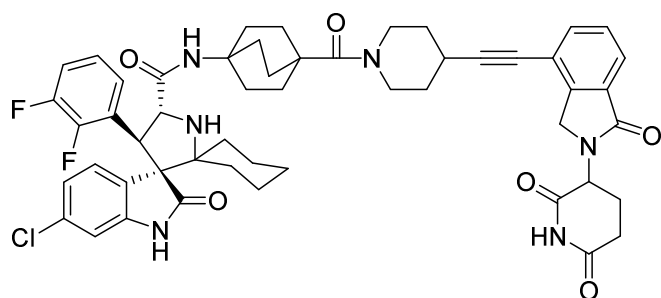
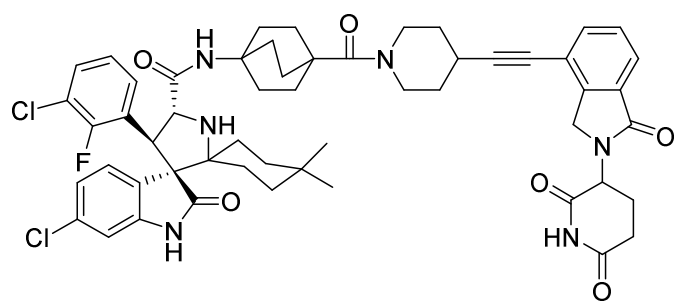
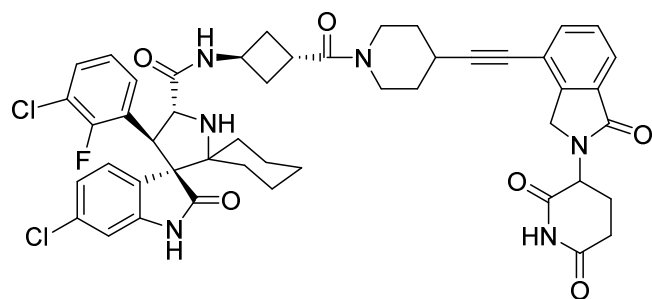
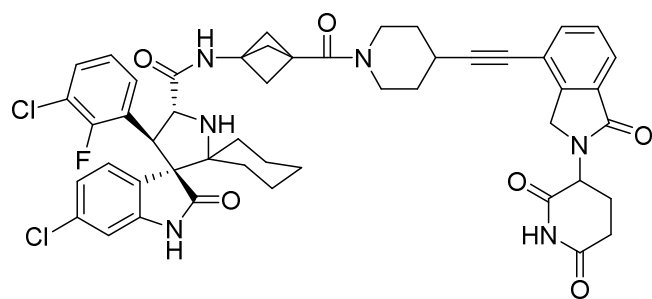
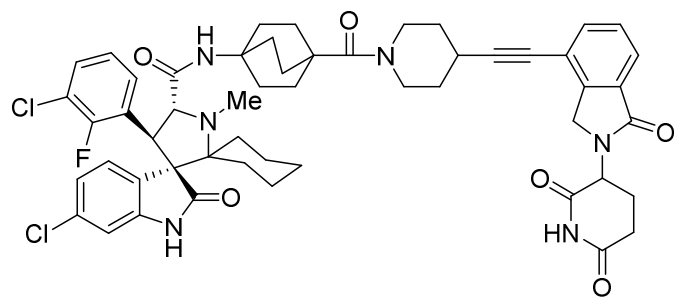


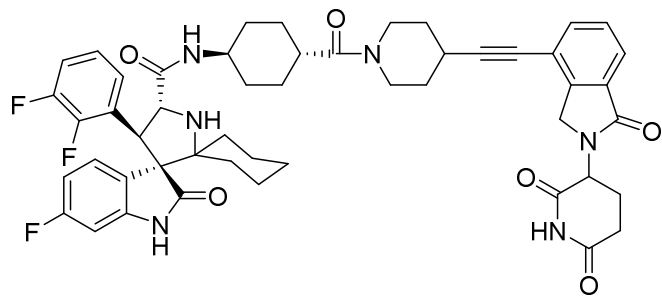
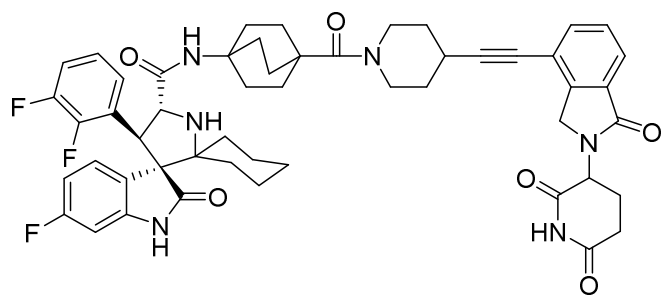
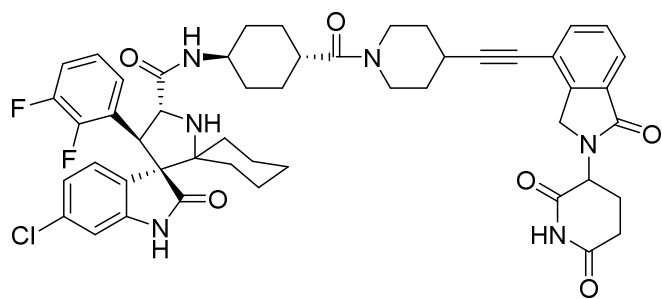
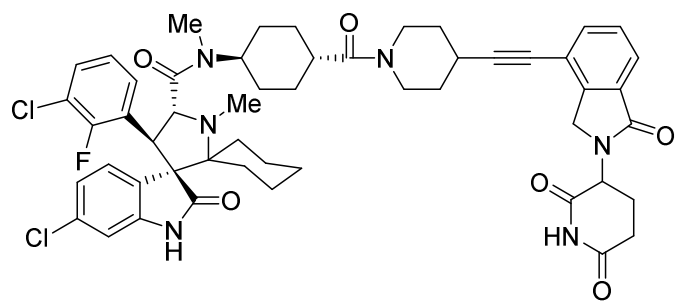
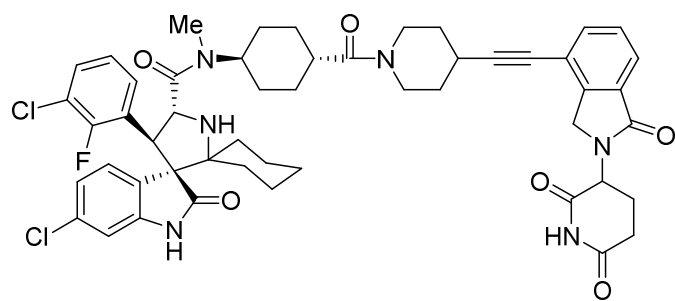
or a pharmaceutically acceptable salt or solvate thereof.

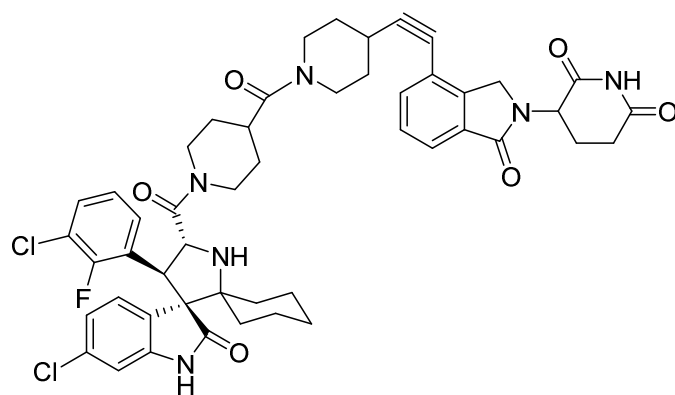
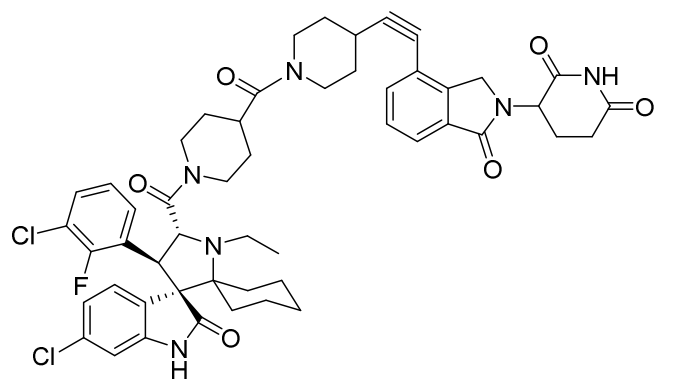
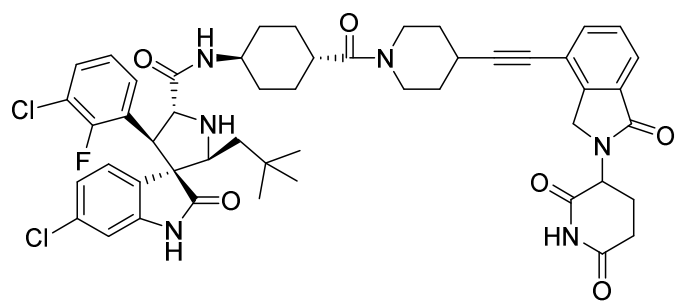
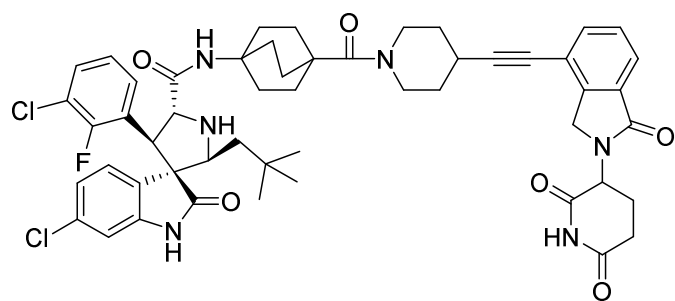
3. The compound of claim 1 selected from the group consisting of

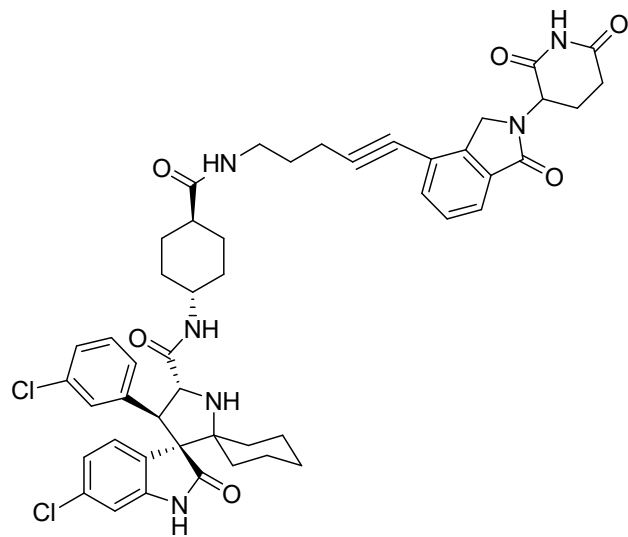
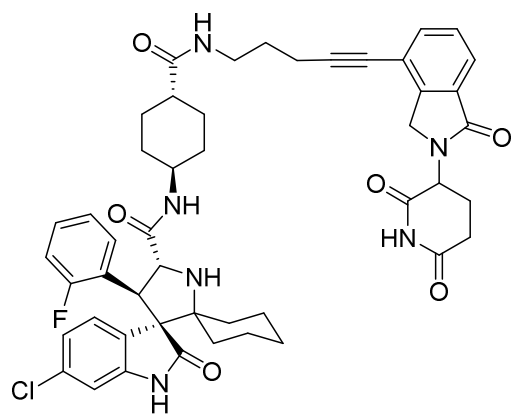
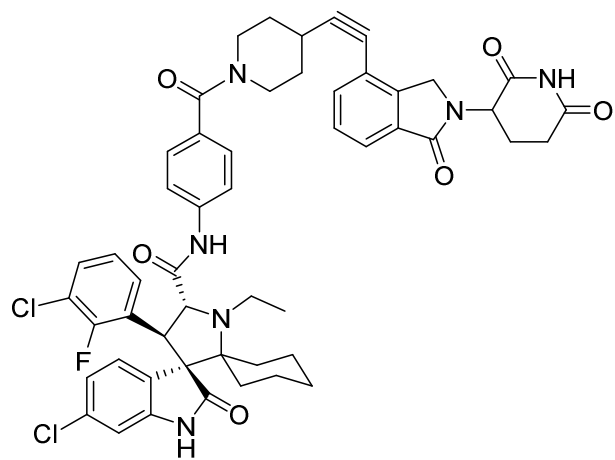


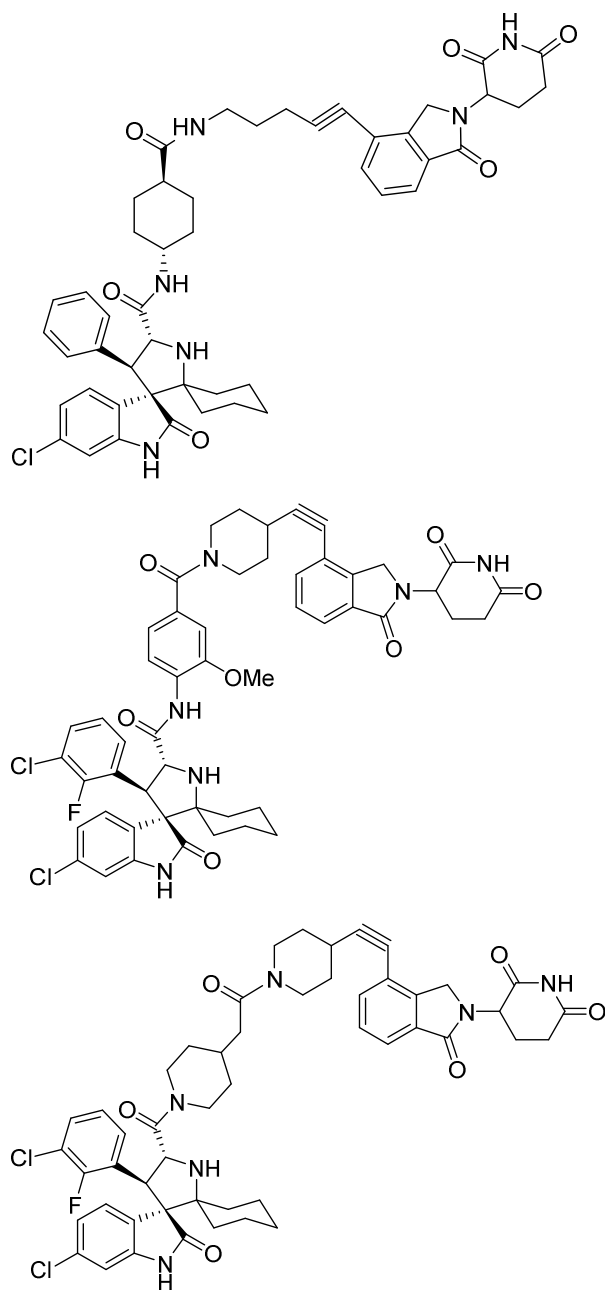


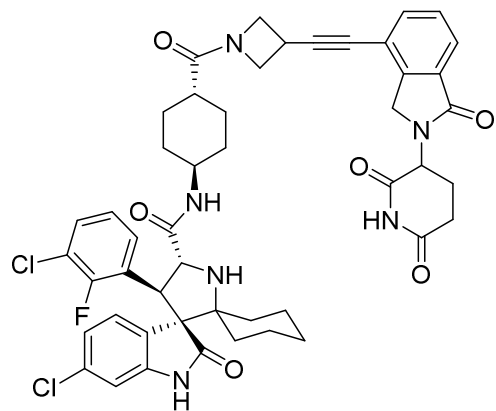
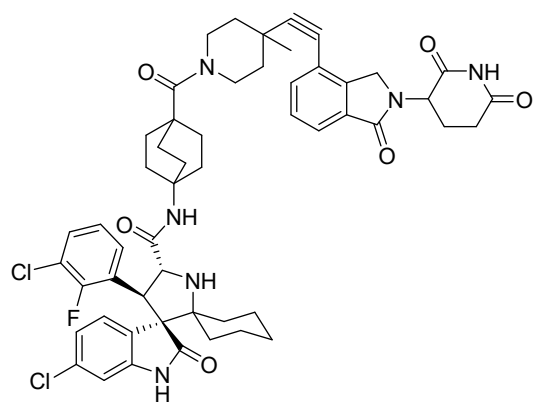
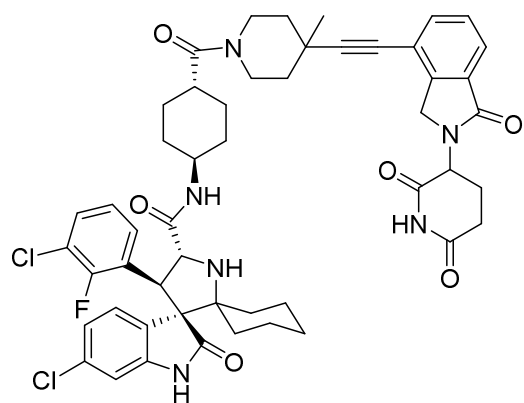


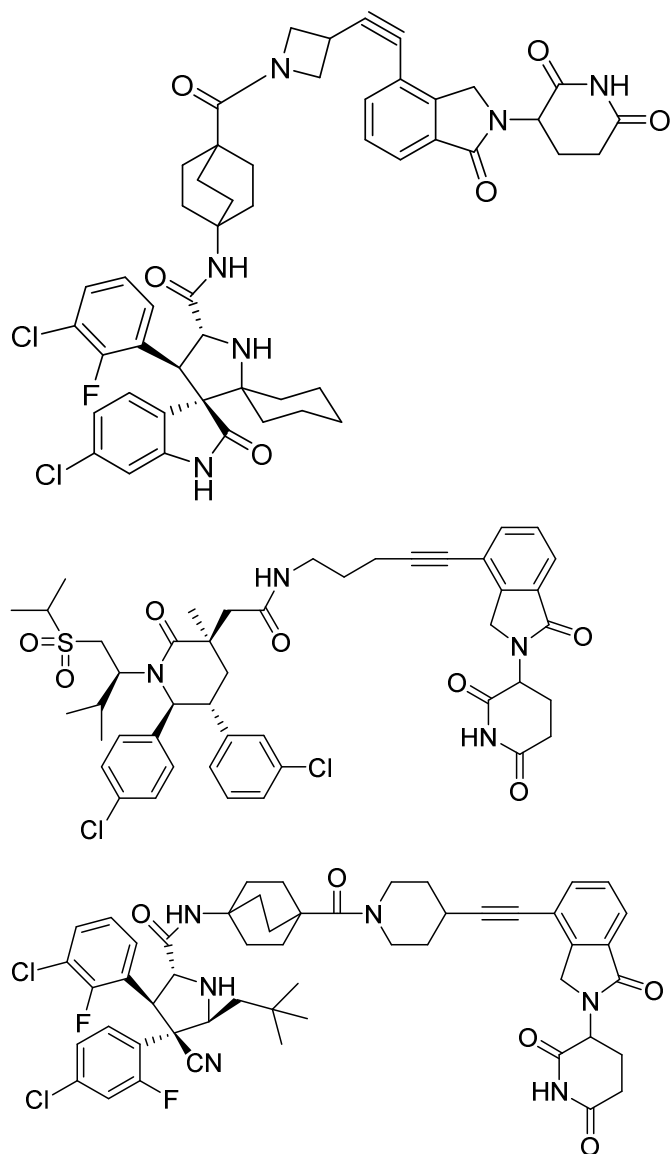












or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 3 that is (3'R,4'S,5'R)-6''-chloro-4'-(3-chloro-2-fluorophenyl)-N-((1r,4R)-4-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)ethynyl)piperidine-1-carbonyl)cyclohexyl)-2''-oxodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indoline]-5'-carboxamide, or a pharmaceutically acceptable salt or solvate thereof.

5. The compound of claim 3 that is (3'R,4'S,5'R)-6''-chloro-4'-(3-chloro-2-fluorophenyl)-N-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)ethynyl)piperidine-1-carbonyl)bicyclo[2.2.2]octan-1-yl)-2''-oxodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indoline]-5'-carboxamide, or a pharmaceutically acceptable salt or solvate thereof.

6. A compound that is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)-N-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)acetamide, or a pharmaceutically acceptable salt or solvate thereof.

7. A compound that is (2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-N-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)ethynyl)piperidine-1-carbonyl)bicyclo[2.2.2]octan-1-yl)-5-neopentylpyrrolidine-2-carboxamide, or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of claim 1, wherein the pharmaceutically acceptable salt is the ethane-1,2-disulfonic acid salt or the naphthalene-1,5-disulfonic acid salt.

9. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

10. A compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, for use in treatment of cancer.

11. Use of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treatment of cancer.

12. The use of claim 11, wherein the cancer is any one or more of the cancers selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma,

basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological cancer, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma,

primary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

13. The use of claim 11, wherein the cancer is a hematological cancer.

14. The use of claim 13, wherein the hematological cancer is any one or more of the cancers of acute lymphocytic leukemia (ALL), acute eosinophilic leukemia, acute myeloid leukemia (AML), acute erythroid leukemia, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia, small lymphocytic lymphoma (SLL), acute megakaryoblastic leukemia, multiple myeloma (MM), acute monocytic leukemia, Hodgkins lymphoma (HL), acute promyelocytic leukemia, non-Hodgkin's lymphoma (NHL), acute myelogenous leukemia, mantle cell lymphoma (MCL), B-cell prolymphocytic leukemia, marginal zone B-cell lymphoma, B-cell lymphoma, splenic marginal zone lymphoma, MALT lymphoma, follicular lymphoma (FL), precursor T-lymphoblastic lymphoma, Waldenstrom's macroglobulinemia (WM), T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mast cell leukemia, marginal zone lymphoma (MZL), adult T cell leukemia/lymphoma, hairy cell leukemia (HCL), aggressive NK-cell leukemia, Burkitt's lymphoma (BL), angioimmunoblastic T-cell lymphoma, and Richter's transformation.

15. A kit comprising the compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or solvate thereof, to a subject having cancer.

16. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a subject having cancer, wherein:

(a) whether an overexpression of MDM2 is present or absent in a biological sample taken from the subject is to be determined; and

(b) a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, is to be administered to the subject if an overexpression of MDM2 is present in the biological sample.

17. Use of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a subject having cancer, wherein the cancer is characterized as having an overexpression of MDM2.

18. The use of claim 14, wherein the hematological cancer is acute lymphocytic leukemia, chronic lymphocytic leukemia, or acute myeloid leukemia.

19. A compound that is 3-(4-((1-((1r,4r)-4-aminocyclohexane-1-carbonyl)piperidin-4-yl)ethynyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione.