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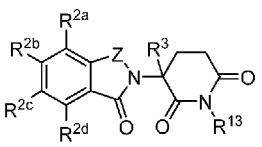
(54) Title: CEREBLON E3 LIGASE INHIBITORS



I,

(57) Abstract: The present disclosure provides compounds represented by Formula I: wherein R2a, R2b, R2c, R2d, R3, R13, and Z are as defined in the specification, and the salts and solvates thereof. Compounds of Formula I are cereblon (CRBN) ubiquitination inhibitors or monofunctional synthetic intermediates that can be used to prepare PROTAC molecules. CRBN ubiquitination inhibitors and PROTAC molecules are useful for the treatment of cancer and other diseases.

CEREBLON E3 LIGASE INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides cereblon (CRBN) ubiquitination inhibitors and therapeutic methods of treating conditions and diseases, e.g., cancer, wherein the inhibition of CRBN ubiquitination provides a benefit.

Background

[0002] Cereblon (CRBN), a component of the DDB1-CUL4a-Roc1 ubiquitin ligase complex, is a molecular target of immunomodulatory agents such as thalidomide, lenalidomide, and pomalidomide. Lopez-Girona et al., *Leukemia 26*:2326-2335 (2012). Inhibition of CRBN ubiquitination by these agents may allow CRBN to accumulate, leading to the increased cullin-4 RING E3 ligase-mediated degradation of target proteins. Liu et al., *FASEB J 12*:4829-4839 (2015). There exists a need for new immunomodulatory agents for the treatment of cancer and other diseases.

BRIEF SUMMARY OF THE INVENTION

[0003] In one aspect, the present disclosure provides compounds represented by any one of Formulae **I-IV**, **IX-XVI**, or **XVIII-XXII**, below, and the pharmaceutically acceptable salts and solvates, e.g., hydrates, thereof, collectively referred to as "Compounds of the Disclosure." Compounds of the Disclosure inhibit CRBN ubiquitination and are thus useful in treating or preventing diseases or conditions such as cancer wherein the inhibition of CRBN ubiquitination provides a benefit. Compounds of the Disclosure may also be synthetic intermediates that are used to prepare CRBN ubiquitination inhibitors. Compounds of the Disclosure may also be synthetic intermediates that are used to prepare targeted-protein degraders.

[0004] In another aspect, the present disclosure provides methods of treating or preventing a condition or disease by administering a therapeutically effective amount of a Compound of the Disclosure to a subject, e.g., a human patient, in need thereof. The disease or condition of interest that is treatable or preventable by inhibition CRBN ubiquitination is, for example, cancer or other proliferative disorder, or an inflammatory

disease. 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, Compounds of the Disclosure may reduce the proliferation of unwanted cells by modulating the function of CRBN in those cells. In some embodiments, Compounds of the Disclosure are administered in combination with an optional therapeutic agent.

[0005] In another aspect, the present disclosure provides a method of inhibiting CRBN ubiquitination in a subject, comprising administering to the subject a therapeutically effective amount of a Compound of the Disclosure.

[0006] In another aspect, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier.

[0007] In another aspect, the present disclosure provides a composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier for use treating or preventing diseases or conditions wherein the inhibition of CRBN ubiquitination provides a benefit, e.g., cancer.

[0008] In another aspect, 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.

[0009] In another aspect, the present disclosure provides a Compound of the Disclosure for use in the treatment or prevention of a disease or condition of interest, e.g., cancer.

[0010] In another aspect, 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.

[0011] In another aspect, the present disclosure provides a kit comprising a Compound of the Disclosure, and, optionally, a packaged composition comprising an optional 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.

[0012] In one aspect, the present disclosure provides compounds represented by any one of Formulae **VI-VIII** or **XVII**, below, and the salts and solvates, e.g., hydrates, thereof,

collectively referred to as "Intermediates of the Disclosure." Intermediates of the Disclosure can be used to prepare Compounds of the Disclosure.

[0013] In another aspect, the present disclosure provides methods of preparing Compounds of the Disclosure.

[0014] In another embodiment, the disclosure provides compounds represented by any one of Formulae **XXIII-XXXIV**, below, and the pharmaceutically acceptable salts and solvates, e.g., hydrates, thereof, collectively referred to as "PROTAC Molecules." A PROTAC molecule is a heterobifunctional small molecule containing a ligand that binds to a target protein of interest and a second ligand for an E3 ligase covalently tethered to one another by a chemical linker.

[0015] In another aspect, the present disclosure provides methods of preparing PROTAC molecules comprising Compounds of the Disclosure.

[0016] 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.

[0017] 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 invention as claimed.

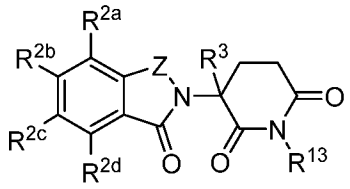
DETAILED DESCRIPTION OF THE INVENTION

I. Compounds of the Disclosure

[0018] Compounds of the Disclosure inhibit the ubiquitination of CRBN. Without wishing to be bound by any particular theory, inhibition of CRBN ubiquitination may allow CRBN to accumulate, leading to the increased cullin-4 RING E3 ligase-mediated degradation of target proteins. *See* Liu *et al.*, *FASEB J 29*:4829-4839 (2015).

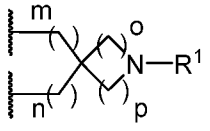
[0019] Compounds of the Disclosure may also be used as monofunctional synthetic intermediates to prepare PROTAC Molecules.

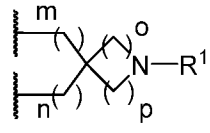
[0020] In one embodiment, Compounds of the Disclosure are compounds of Formula **I**:

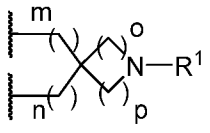


I,

wherein:

[0021] R^{2b} and R^{2c} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; or

[0022] R^{2a} and R^{2b} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; or

[0023] R^{2c} and R^{2d} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

[0024] R^3 is selected from the group consisting of hydrogen, deuterium, fluoro, and C_1-C_3 alkyl;

[0025] m is 1, 2, or 3;

[0026] n is 1, 2, or 3;

[0027] o is 1, 2, or 3;

[0028] p is 1, 2, or 3;

[0029] Z is selected from the group consisting of $-CR^{8a}R^{8b}-$ and -C(=O)-;

[0030] R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl,

optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$;

[0031] R^{1a} is selected from the group consisting of hydrogen, -OH, -CHO, -C(=O)OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$;

[0032] R^{1b} is selected from the group consisting of hydrogen and C_1-C_3 alkyl; or

[0033] R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a -C(=O)-;

[0034] R^4 is selected from the group consisting of $-R^{4a}$, $-OR^{4b}$, and $-NR^{4c}R^{4d}$;

[0035] R^5 is selected from the group consisting of $-R^{5a}$ and $-NR^{5a}R^{5b}$;

[0036] R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and cyano;

[0037] R^7 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and $-NR^{7a}R^{7b}$;

[0038] R^{4a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

[0039] R^{4b} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

[0040] R^{4c} and R^{4d} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

[0041] R^{4c} and R^{4d} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo;

[0042] R^{5a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

[0043] R^{5b} and R^{5c} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

[0044] R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

[0045] R^{7a} and R^{7b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo;

[0046] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and C_1-C_3 alkyl; or

[0047] R^{8a} and R^{8b} taken together with the carbon atom to which they are attached from a C_3-C_6 cycloalkyl; and

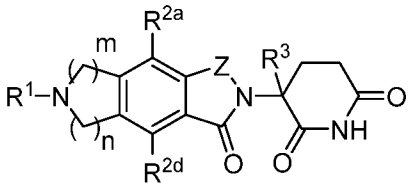
[0048] R^{13} is selected from the group consisting of hydrogen and C_1-C_3 alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0049] In another embodiment, Compounds of the Disclosure are compounds of Formula **I**, wherein Z is selected from the group consisting of -CH_2- and -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0050] In another embodiment, Compounds of the Disclosure are compounds of Formula **I**, wherein R^{13} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0051] In another embodiment, Compounds of the Disclosure are compounds of Formula **I**, wherein R^{13} is methyl, or a pharmaceutically acceptable salt or solvate thereof.

[0052] In another embodiment, Compounds of the Disclosure are compounds of Formula **II**:



II,

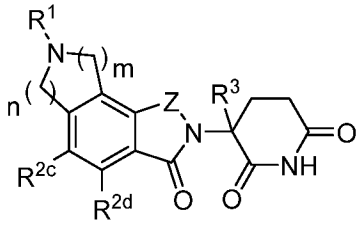
wherein R^1, R^{2a}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0053] In another embodiment, Compounds of the Disclosure are compounds of Formula **II**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0054] In another embodiment, Compounds of the Disclosure are compounds of Formula **II**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0055] In another embodiment, Compounds of the Disclosure are compounds of Formula **II**, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2d} are hydrogen.

[0056] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**:



III,

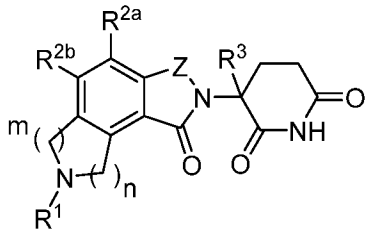
wherein R^1, R^{2c}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0057] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0058] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0059] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2c} and R^{2d} are hydrogen.

[0060] In another embodiment, Compounds of the Disclosure are compounds of Formula **IV**:



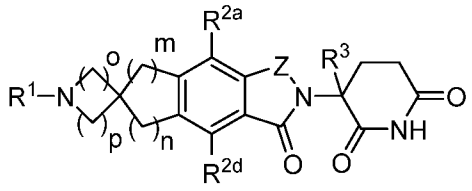
IV,

wherein R^1, R^{2a}, R^{2b}, R^3, m, and n are as defined in connection with Formula **I**; and Z is -$CR^{8a}R^{8b}$-, or a pharmaceutically acceptable salt or solvate thereof.

[0061] In another embodiment, Compounds of the Disclosure are compounds of Formula **IV**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0062] In another embodiment, Compounds of the Disclosure are compounds of Formula **IV**, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2b} are hydrogen.

[0063] In another embodiment, Compounds of the Disclosure are compounds of Formula **IX**:



IX,

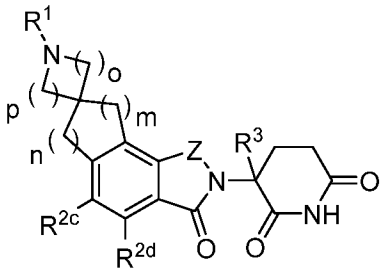
wherein R^1, R^{2a}, R^{2d}, R^3, m, n, o, p, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0064] In another embodiment, Compounds of the Disclosure are compounds of Formula **IX**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0065] In another embodiment, Compounds of the Disclosure are compounds of Formula **IX**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0066] In another embodiment, Compounds of the Disclosure are compounds of Formula **IX**, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2d} are hydrogen.

[0067] In another embodiment, Compounds of the Disclosure are compounds of Formula **X**:



X,

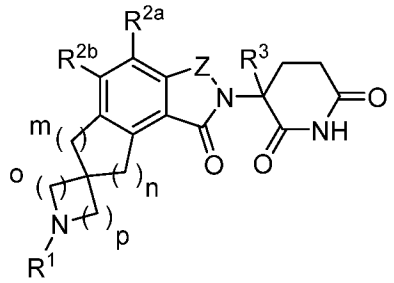
wherein R^1, R^{2c}, R^{2d}, R^3, m, n, o, p, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0068] In another embodiment, Compounds of the Disclosure are compounds of Formula **X**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0069] In another embodiment, Compounds of the Disclosure are compounds of Formula **X**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0070] In another embodiment, Compounds of the Disclosure are compounds of Formula **X**, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2c} and R^{2d} are hydrogen.

[0071] In another embodiment, Compounds of the Disclosure are compounds of Formula **XI**:



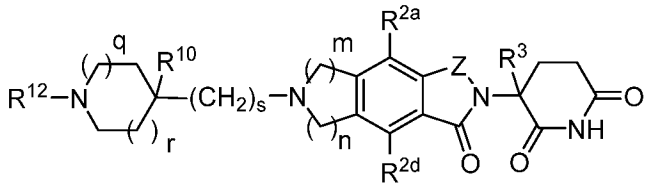
XI,

wherein R^1, R^{2a}, R^{2b}, R^3, m, n, o, and p are as defined in connection with Formula **I**; and Z is -$CR^{8a}R^{8b}$-, or a pharmaceutically acceptable salt or solvate thereof.

[0072] In another embodiment, Compounds of the Disclosure are compounds of Formula **XI**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0073] In another embodiment, Compounds of the Disclosure are compounds of Formula **XI**, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2b} are hydrogen.

[0074] In another embodiment, Compounds of the Disclosure are compounds of Formula **XII**:



XII,

wherein:

[0075] q and r are independently 0, 1, or 2;

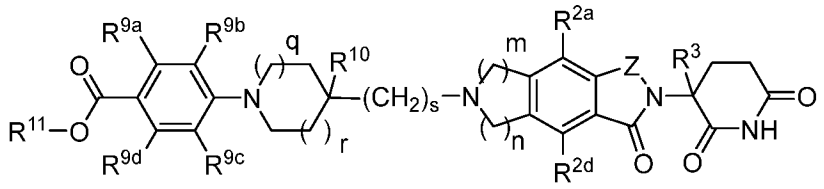
[0076] s is 0 or 1;

[0077] R^{10} is selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

[0078] R^{12} is selected from the group consisting of hydrogen, optionally substituted heterocyclo, and optionally substituted phenyl; and

[0079] R^{2a}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0080] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIII**:



XIII,

wherein:

[0081] q and r are independently 0, 1, or 2;

[0082] s is 0 or 1;

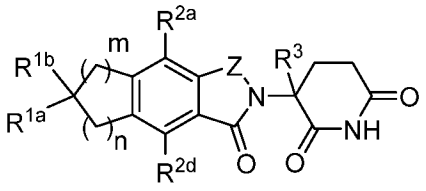
[0083] R^{9a}, R^{9b}, R^{9c}, and R^{9d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and C_1-C_3 alkoxy;

[0084] R^{10} is selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

[0085] R^{11} is selected from the group consisting of hydrogen and C_1-C_6 alkyl; and

[0086] R^{2a}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0087] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIV**:



XIV,

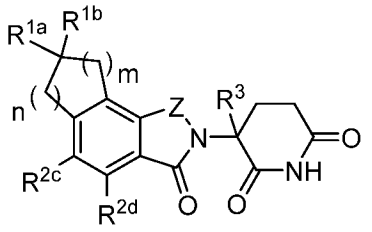
wherein R^{1a}, R^{1b}, R^{2a}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0088] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIV**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0089] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIV**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0090] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIV**, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2d} are hydrogen.

[0091] In another embodiment, Compounds of the Disclosure are compounds of Formula **XV**:



XV,

wherein R^{1a}, R^{1b}, R^{2c}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

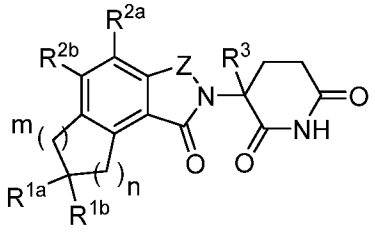
[0092] In another embodiment, Compounds of the Disclosure are compounds of Formula **XV**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0093] In another embodiment, Compounds of the Disclosure are compounds of Formula **XV**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0094] In another embodiment, Compounds of the Disclosure are compounds of Formula **XV**, wherein R^{2c} and R^{2d} are independently selected from the group consisting

of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2c} and R^{2d} are hydrogen.

[0095] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVI**:



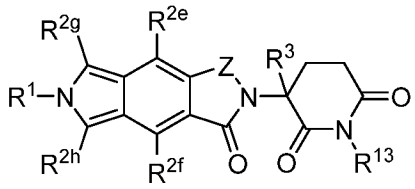
XVI,

wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, m, and n are as defined in connection with Formula **I**; and Z is $-CR^{8a}R^{8b}-$, or a pharmaceutically acceptable salt or solvate thereof.

[0096] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVI**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0097] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVI**, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2b} are hydrogen.

[0098] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVIII**:



XVIII,

wherein:

R^{2e}, R^{2f}, R^{2g}, and R^{2h} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; and

R^1, R^3, R^{13}, and Z as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

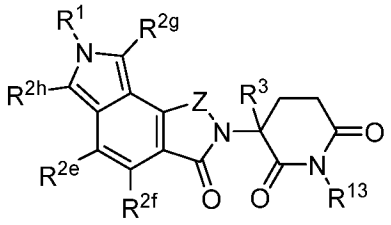
[0099] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVIII**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0100] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVIII**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0101] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVIII**, wherein R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen and halo, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2e} and R^{2f} are hydrogen.

[0102] In another embodiment, Compounds of the Disclosure are compounds of Formula **XVIII**, wherein R^{2g} and R^{2h} are independently selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2g} and R^{2h} are hydrogen.

[0103] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIX**:



XIX,

wherein:

[0104] R^{2e}, R^{2f}, R^{2g}, and R^{2h} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; and

[0105] R^1, R^3, R^{13}, and Z as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

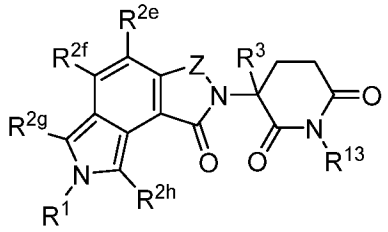
[0106] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIX**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0107] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIX**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0108] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIX**, wherein R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen and halo, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2e} and R^{2f} are hydrogen.

[0109] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIX**, wherein R^{2g} and R^{2h} are independently selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2g} and R^{2h} are hydrogen

[0110] In another embodiment, Compounds of the Disclosure are compounds of Formula **XX**:



XX,

wherein:

[0111] R^{2e}, R^{2f}, R^{2g}, and R^{2h} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

[0112] Z is $-CR^{8a}R^{8b}-$; and

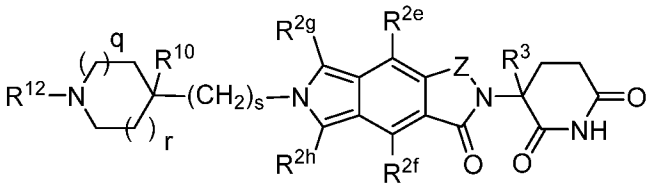
[0113] R^1, R^3, and R^{13} as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0114] In another embodiment, Compounds of the Disclosure are compounds of Formula **XX**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0115] In another embodiment, Compounds of the Disclosure are compounds of Formula **XX**, wherein R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen and halo, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2e} and R^{2f} are hydrogen.

[0116] In another embodiment, Compounds of the Disclosure are compounds of Formula **XX**, wherein R^{2g} and R^{2h} are independently selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2g} and R^{2h} are hydrogen.

[0117] In another embodiment, Compounds of the Disclosure are compounds of Formula **XXI**:



XXI,

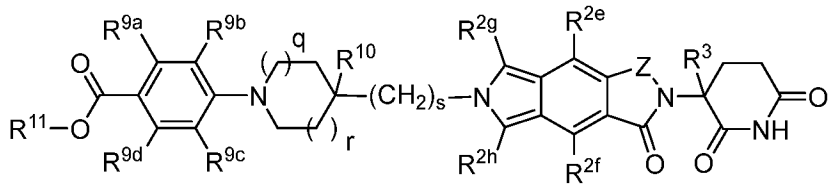
wherein:

[0118] R^{2e}, R^{2f}, R^{2g}, and R^{2h} are as defined in connection with Formula **XVIII**;

[0119] q, r, s, R^{10}, and R^{12}, are as defined in connection with Formula **XII**; and

[0120] R^3 and Z as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0121] In another embodiment, Compounds of the Disclosure are compounds of Formula **XXII**:



XXII,

wherein:

[0122] R^{2e}, R^{2f}, R^{2g}, and R^{2h} are as defined in connection with Formula **XVIII**;

[0123] q, r, s, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{10}, R^{11}, and R^{12} are as defined in connection with Formula **XIII**; and

[0124] R^3 and Z as defined in connection with Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0125] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XVI**, or **XVIII-XXII**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXIV**, *see* below, wherein R^3 is selected from the group consisting of hydrogen, deuterium, fluoro, and methyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^3 is hydrogen. In another embodiment, R^3 is deuterium. In another embodiment, R^3 is fluoro. In another embodiment, R^3 is methyl.

[0126] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein m is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0127] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein m is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0128] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of

Formula **XXIII-XXXI**, wherein m is 3, or a pharmaceutically acceptable salt or solvate thereof.

[0129] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein n is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0130] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein n is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0131] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein n is 3, or a pharmaceutically acceptable salt or solvate thereof

[0132] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein m is 1 and n is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0133] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, *see* below, wherein m is 1 and n is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0134] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein m is 2 and n is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0135] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein m is 2 and n is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0136] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein m is 1 and n is 3, or a pharmaceutically acceptable salt or solvate thereof.

[0137] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XVI**, and PROTAC Molecules are compounds of any one of Formula **XXIII-XXXI**, wherein m is 3 and n is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0138] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0139] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **XIV-XVI**, wherein R^{1a} is selected from the group consisting of -OH, -CHO, $-CH_2OH$, and -C(=O)OH; and R^{1b} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0140] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **XIV-XVI**, wherein R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0141] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IX-XI**, and PROTAC Molecules are compounds of any one of Formula **XXVI-XXVIII**, wherein o is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0142] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IX-XI**, and PROTAC Molecules are compounds of any one of Formula **XXVI-XXVIII**, wherein o is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0143] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I IX-XI**, and PROTAC Molecules are compounds of any one of Formula **XXVI-XXVIII**, wherein p is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0144] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IX-XI**, and PROTAC Molecules are compounds of any one of Formula **XXVI-XXVIII**, wherein p is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0145] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IX-XI**, and PROTAC Molecules are compounds of any one of

Formula **XXVI-XXVIII**, wherein o is 1 and p is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0146] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IX-XI**, and PROTAC Molecules are compounds of any one of Formula **XXVI-XXVIII**, wherein o is 1 and p is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0147] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IX-XI**, and PROTAC Molecules are compounds of any one of Formula **XXVI-XXVIII**, wherein o is 2 and p is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0148] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IX-XI**, and PROTAC Molecules are compounds of any one of Formula **XXVI-XXVIII**, *see* below, wherein o is 2 and p is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0149] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, optionally substituted C_3-C_8 cycloalkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0150] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is C_1-C_6 alkyl, or a pharmaceutically acceptable salt or solvate thereof.

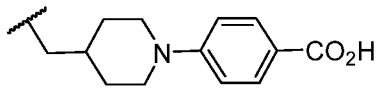
[0151] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is optionally substituted C_1-C_6 alkyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^1 is carboxyalkyl, e.g., $-CH_2C(=O)OH$.

[0152] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVII-XX**, wherein R^1 is C_1-C_6 haloalkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0153] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is optionally substituted C_3-C_8 cycloalkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0154] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is selected from the group consisting of (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl,

(heteroaryl)alkyl, and aralkyl, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, R^1 is (heterocyclo)alkyl, e.g.,  .

[0155] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is (hydroxy)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0156] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is (amino)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0157] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is (alkoxy)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0158] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV** or **IX-XI**, w **I-IV**, **IX-XI**, or **XVIII-XX**, herein R^1 is (cycloalkyl)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

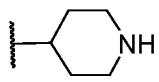
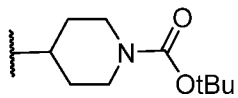
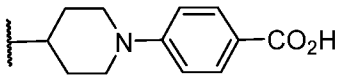
[0159] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is (heterocyclo)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0160] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is (heteroaryl)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0161] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is aralkyl, or a pharmaceutically acceptable salt or solvate thereof.

[0162] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is selected from the group consisting of optionally substituted 4- to 8-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

[0163] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is selected from the group consisting of optionally substituted 4- to 8-membered heterocyclo. In another embodiment, R^1 is optionally substituted 4-membered heterocyclo. In another embodiment, R^1 is optionally substituted 5-membered heterocyclo. In another embodiment, R^1 is optionally substituted

6-membered heterocyclo, e.g.,  ,  , or  .

[0164] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is optionally substituted 4- to 8-membered heterocyclo, or a pharmaceutically acceptable salt or solvate thereof.

[0165] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is optionally substituted aryl, or a pharmaceutically acceptable salt or solvate thereof.

[0166] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is optionally substituted heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

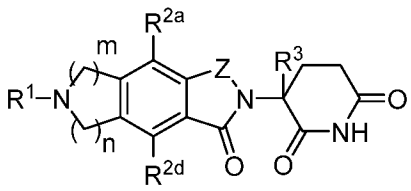
[0167] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is $-C(=O)R^4$, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^4 is $-R^{4a}$. In another embodiment, R^4 is $-OR^{4b}$. In another embodiment, R^{4b} is C_1-C_6 alkyl. In another embodiment, R^4 is $-NR^{4c}R^{4d}$;

[0168] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is $-S(=O)_2R^5$, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^5 is $-R^{5a}$. In another embodiment, R^{5a} is C_1-C_6 alkyl. In another embodiment, R^5 is $-NR^{5b}R^{5c}$.

[0169] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-IV**, **IX-XI**, or **XVIII-XX**, wherein R^1 is $-C(=NR^6)R^7$, or a pharmaceutically acceptable salt or solvate thereof.

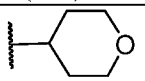
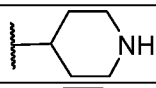
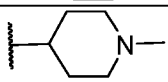
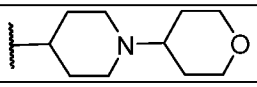
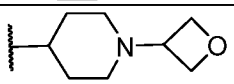
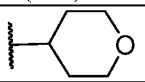
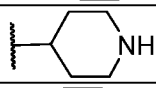
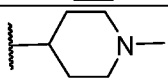
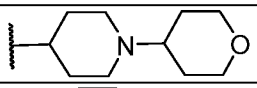
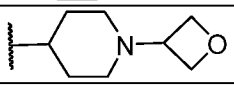
[0170] In another embodiment, Compounds of the Disclosure are compounds of Formula **II**, wherein R^1, R^{2a}, R^{2d}, R^3, m, n, and Z are as defined in Table 1, or a pharmaceutically acceptable salt or solvate thereof.

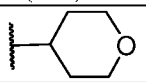
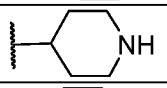
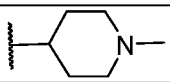
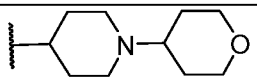
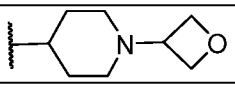
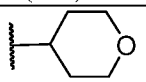
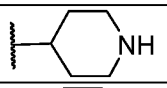
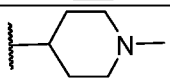
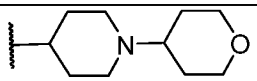
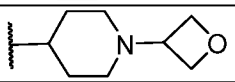
Table 1



II

Cpd.	R^1	R^{2a}	R^{2d}	R^3	m	n	Z

No.							
1	-H	-H	-H	-H	1	1	$-CH_2-$
2	$-CH_3$	-H	-H	-H	1	1	$-CH_2-$
3	$-CH_2CH_3$	-H	-H	-H	1	1	$-CH_2-$
4	$-CH(CH_3)$	-H	-H	-H	1	1	$-CH_2-$
5	$-CH_2CH(CH_3)$	-H	-H	-H	1	1	$-CH_2-$
6	$-C(=O)CH_3$	-H	-H	-H	1	1	$-CH_2-$
7	$-C(=O)CF_3$	-H	-H	-H	1	1	$-CH_2-$
8	$-C(=O)OCH_3$	-H	-H	-H	1	1	$-CH_2-$
9	$-C(=O)OC(CH_3)_3$	-H	-H	-H	1	1	$-CH_2-$
10	$-S(=O)_2CH_3$	-H	-H	-H	1	1	$-CH_2-$
11		-H	-H	-H	1	1	$-CH_2-$
12		-H	-H	-H	1	1	$-CH_2-$
13		-H	-H	-H	1	1	$-CH_2-$
14		-H	-H	-H	1	1	$-CH_2-$
15		-H	-H	-H	1	1	$-CH_2-$
16	-H	-H	-H	-F	1	1	$-CH_2-$
17	$-CH_3$	-H	-H	-F	1	1	$-CH_2-$
18	$-CH_2CH_3$	-H	-H	-F	1	1	$-CH_2-$
19	$-CH(CH_3)$	-H	-H	-F	1	1	$-CH_2-$
20	$-CH_2CH(CH_3)$	-H	-H	-F	1	1	$-CH_2-$
21	$-C(=O)CH_3$	-H	-H	-F	1	1	$-CH_2-$
22	$-C(=O)CF_3$	-H	-H	-F	1	1	$-CH_2-$
23	$-C(=O)OCH_3$	-H	-H	-F	1	1	$-CH_2-$
24	$-C(=O)OC(CH_3)_3$	-H	-H	-F	1	1	$-CH_2-$
25	$-S(=O)_2CH_3$	-H	-H	-F	1	1	$-CH_2-$
26		-H	-H	-F	1	1	$-CH_2-$
27		-H	-H	-F	1	1	$-CH_2-$
28		-H	-H	-F	1	1	$-CH_2-$
29		-H	-H	-F	1	1	$-CH_2-$
30		-H	-H	-F	1	1	$-CH_2-$
31	-H	-H	-H	$-CH_3$	1	1	$-CH_2-$
32	$-CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
33	$-CH_2CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
34	$-CH(CH_3)$	-H	-H	$-CH_3$	1	1	$-CH_2-$
35	$-CH_2CH(CH_3)$	-H	-H	$-CH_3$	1	1	$-CH_2-$
36	$-C(=O)CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
37	$-C(=O)CF_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$

38	$-C(=O)OCH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
39	$-C(=O)OC(CH_3)_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
40	$-S(=O)_2CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
41		-H	-H	$-CH_3$	1	1	$-CH_2-$
42		-H	-H	$-CH_3$	1	1	$-CH_2-$
43		-H	-H	$-CH_3$	1	1	$-CH_2-$
44		-H	-H	$-CH_3$	1	1	$-CH_2-$
45		-H	-H	$-CH_3$	1	1	$-CH_2-$
46	-H	-H	-H	-D	1	1	$-CH_2-$
47	$-CH_3$	-H	-H	-D	1	1	$-CH_2-$
48	$-CH_2CH_3$	-H	-H	-D	1	1	$-CH_2-$
49	$-CH(CH_3)$	-H	-H	-D	1	1	$-CH_2-$
50	$-CH_2CH(CH_3)$	-H	-H	-D	1	1	$-CH_2-$
51	$-C(=O)CH_3$	-H	-H	-D	1	1	$-CH_2-$
52	$-C(=O)CF_3$	-H	-H	-D	1	1	$-CH_2-$
53	$-C(=O)OCH_3$	-H	-H	-D	1	1	$-CH_2-$
54	$-C(=O)OC(CH_3)_3$	-H	-H	-D	1	1	$-CH_2-$
55	$-S(=O)_2CH_3$	-H	-H	-D	1	1	$-CH_2-$
56		-H	-H	-D	1	1	$-CH_2-$
57		-H	-H	-D	1	1	$-CH_2-$
58		-H	-H	-D	1	1	$-CH_2-$
59		-H	-H	-D	1	1	$-CH_2-$
60		-H	-H	-D	1	1	$-CH_2-$
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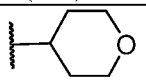
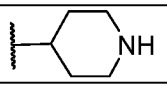
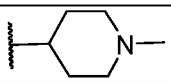
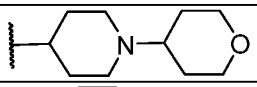
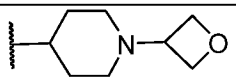
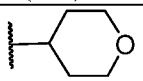
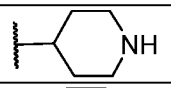
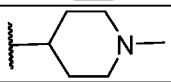
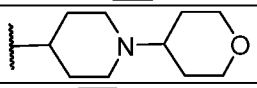
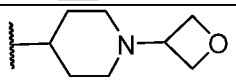
62	$-CH_3$	-H	-H	-H	2	1	$-CH_2-$
63	$-CH_2CH_3$	-H	-H	-H	2	1	$-CH_2-$
64	$-CH(CH_3)$	-H	-H	-H	2	1	$-CH_2-$
65	$-CH_2CH(CH_3)$	-H	-H	-H	2	1	$-CH_2-$
66	$-C(=O)CH_3$	-H	-H	-H	2	1	$-CH_2-$
67	$-C(=O)CF_3$	-H	-H	-H	2	1	$-CH_2-$
68	$-C(=O)OCH_3$	-H	-H	-H	2	1	$-CH_2-$
69	$-C(=O)OC(CH_3)_3$	-H	-H	-H	2	1	$-CH_2-$
70	$-S(=O)_2CH_3$	-H	-H	-H	2	1	$-CH_2-$
71		-H	-H	-H	2	1	$-CH_2-$
72		-H	-H	-H	2	1	$-CH_2-$

73		-H	-H	-H	2	1	-CH_2-
74		-H	-H	-H	2	1	-CH_2-
75		-H	-H	-H	2	1	-CH_2-
76	-H	-H	-H	-F	2	1	-CH_2-
77	-CH_3	-H	-H	-F	2	1	-CH_2-
78	-CH_2CH_3	-H	-H	-F	2	1	-CH_2-
79	-$CH(CH_3)$	-H	-H	-F	2	1	-CH_2-
80	-$CH_2CH(CH_3)$	-H	-H	-F	2	1	-CH_2-
81	-$C(=O)CH_3$	-H	-H	-F	2	1	-CH_2-
82	-$C(=O)CF_3$	-H	-H	-F	2	1	-CH_2-
83	-$C(=O)OCH_3$	-H	-H	-F	2	1	-CH_2-
84	-$C(=O)OC(CH_3)_3$	-H	-H	-F	2	1	-CH_2-
85	-$S(=O)_2CH_3$	-H	-H	-F	2	1	-CH_2-
86		-H	-H	-F	2	1	-CH_2-
87		-H	-H	-F	2	1	-CH_2-
88		-H	-H	-F	2	1	-CH_2-
89		-H	-H	-F	2	1	-CH_2-
90		-H	-H	-F	2	1	-CH_2-
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92	-CH_3	-H	-H	-CH_3	2	1	-CH_2-
93	-CH_2CH_3	-H	-H	-CH_3	2	1	-CH_2-
94	-$CH(CH_3)$	-H	-H	-CH_3	2	1	-CH_2-
95	-$CH_2CH(CH_3)$	-H	-H	-CH_3	2	1	-CH_2-
96	-$C(=O)CH_3$	-H	-H	-CH_3	2	1	-CH_2-
97	-$C(=O)CF_3$	-H	-H	-CH_3	2	1	-CH_2-
98	-$C(=O)OCH_3$	-H	-H	-CH_3	2	1	-CH_2-
99	-$C(=O)OC(CH_3)_3$	-H	-H	-CH_3	2	1	-CH_2-
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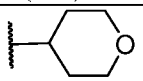
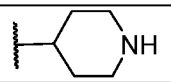
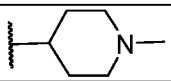
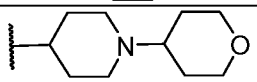
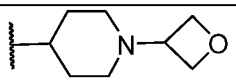
101		-H	-H	-CH_3	2	1	-CH_2-
102		-H	-H	-CH_3	2	1	-CH_2-
103		-H	-H	-CH_3	2	1	-CH_2-
104		-H	-H	-CH_3	2	1	-CH_2-
105		-H	-H	-CH_3	2	1	-CH_2-
106	-H	-H	-H	-D	2	1	-CH_2-
107	-CH_3	-H	-H	-D	2	1	-CH_2-

108	$-CH_2CH_3$	-H	-H	-D	2	1	$-CH_2-$
109	$-CH(CH_3)$	-H	-H	-D	2	1	$-CH_2-$
110	$-CH_2CH(CH_3)$	-H	-H	-D	2	1	$-CH_2-$
111	$-C(=O)CH_3$	-H	-H	-D	2	1	$-CH_2-$
112	$-C(=O)CF_3$	-H	-H	-D	2	1	$-CH_2-$
113	$-C(=O)OCH_3$	-H	-H	-D	2	1	$-CH_2-$
114	$-C(=O)OC(CH_3)_3$	-H	-H	-D	2	1	$-CH_2-$
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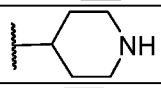
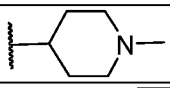
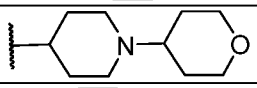
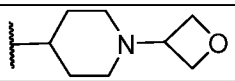
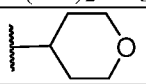
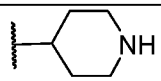
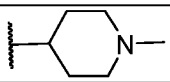
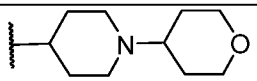
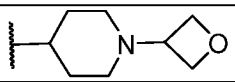
116		-H	-H	-D	2	1	$-CH_2-$
117		-H	-H	-D	2	1	$-CH_2-$
118		-H	-H	-D	2	1	$-CH_2-$
119		-H	-H	-D	2	1	$-CH_2-$
120		-H	-H	-D	2	1	$-CH_2-$
121	-H	-H	-H	-H	1	2	$-CH_2-$
122	$-CH_3$	-H	-H	-H	1	2	$-CH_2-$
123	$-CH_2CH_3$	-H	-H	-H	1	2	$-CH_2-$
124	$-CH(CH_3)$	-H	-H	-H	1	2	$-CH_2-$
125	$-CH_2CH(CH_3)$	-H	-H	-H	1	2	$-CH_2-$
126	$-C(=O)CH_3$	-H	-H	-H	1	2	$-CH_2-$
127	$-C(=O)CF_3$	-H	-H	-H	1	2	$-CH_2-$
128	$-C(=O)OCH_3$	-H	-H	-H	1	2	$-CH_2-$
129	$-C(=O)OC(CH_3)_3$	-H	-H	-H	1	2	$-CH_2-$
130	$-S(=O)_2CH_3$	-H	-H	-H	1	2	$-CH_2-$
131		-H	-H	-H	1	2	$-CH_2-$
132		-H	-H	-H	1	2	$-CH_2-$
133		-H	-H	-H	1	2	$-CH_2-$
134		-H	-H	-H	1	2	$-CH_2-$
135		-H	-H	-H	1	2	$-CH_2-$
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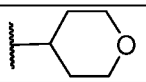
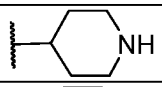
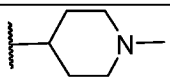
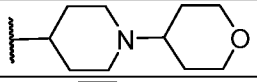
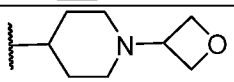
137	$-CH_3$	-H	-H	-F	1	2	$-CH_2-$
138	$-CH_2CH_3$	-H	-H	-F	1	2	$-CH_2-$
139	$-CH(CH_3)$	-H	-H	-F	1	2	$-CH_2-$
140	$-CH_2CH(CH_3)$	-H	-H	-F	1	2	$-CH_2-$
141	$-C(=O)CH_3$	-H	-H	-F	1	2	$-CH_2-$
142	$-C(=O)CF_3$	-H	-H	-F	1	2	$-CH_2-$
143	$-C(=O)OCH_3$	-H	-H	-F	1	2	$-CH_2-$
144	$-C(=O)OC(CH_3)_3$	-H	-H	-F	1	2	$-CH_2-$
145	$-S(=O)_2CH_3$	-H	-H	-F	1	2	$-CH_2-$

146		-H	-H	-F	1	2	-CH_2-
147		-H	-H	-F	1	2	-CH_2-
148		-H	-H	-F	1	2	-CH_2-
149		-H	-H	-F	1	2	-CH_2-
150		-H	-H	-F	1	2	-CH_2-
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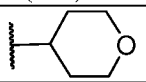
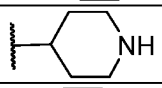
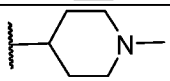
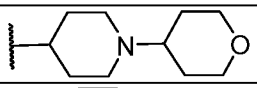
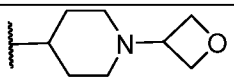
153	-CH_2CH_3	-H	-H	-CH_3	1	2	-CH_2-
154	-$CH(CH_3)$	-H	-H	-CH_3	1	2	-CH_2-
155	-$CH_2CH(CH_3)$	-H	-H	-CH_3	1	2	-CH_2-
156	-$C(=O)CH_3$	-H	-H	-CH_3	1	2	-CH_2-
157	-$C(=O)CF_3$	-H	-H	-CH_3	1	2	-CH_2-
158	-$C(=O)OCH_3$	-H	-H	-CH_3	1	2	-CH_2-
159	-$C(=O)OC(CH_3)_3$	-H	-H	-CH_3	1	2	-CH_2-
160	-$S(=O)_2CH_3$	-H	-H	-CH_3	1	2	-CH_2-
161		-H	-H	-CH_3	1	2	-CH_2-
162		-H	-H	-CH_3	1	2	-CH_2-
163		-H	-H	-CH_3	1	2	-CH_2-
164		-H	-H	-CH_3	1	2	-CH_2-
165		-H	-H	-CH_3	1	2	-CH_2-
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167	-CH_3	-H	-H	-D	1	2	-CH_2-
168	-CH_2CH_3	-H	-H	-D	1	2	-CH_2-
169	-$CH(CH_3)$	-H	-H	-D	1	2	-CH_2-
170	-$CH_2CH(CH_3)$	-H	-H	-D	1	2	-CH_2-
171	-$C(=O)CH_3$	-H	-H	-D	1	2	-CH_2-
172	-$C(=O)CF_3$	-H	-H	-D	1	2	-CH_2-
173	-$C(=O)OCH_3$	-H	-H	-D	1	2	-CH_2-
174	-$C(=O)OC(CH_3)_3$	-H	-H	-D	1	2	-CH_2-
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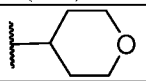
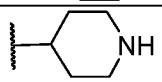
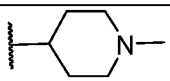
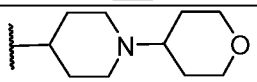
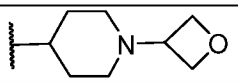
176		-H	-H	-D	1	2	-CH_2-
177		-H	-H	-D	1	2	-CH_2-
178		-H	-H	-D	1	2	-CH_2-
179		-H	-H	-D	1	2	-CH_2-

180		-H	-H	-D	1	2	-CH_2-
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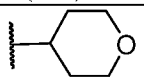
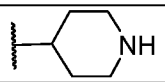
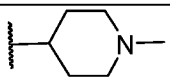
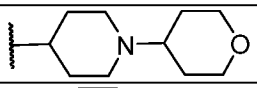
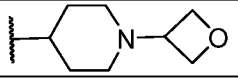
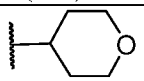
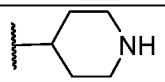
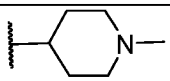
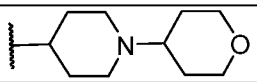
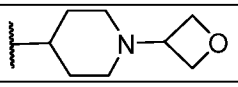
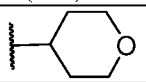
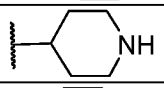
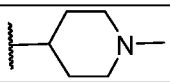
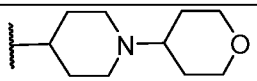
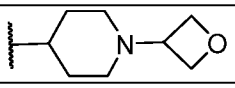
182	-CH_3	-H	-H	-H	1	1	-C(=O)-
183	-CH_2CH_3	-H	-H	-H	1	1	-C(=O)-
184	-$CH(CH_3)$	-H	-H	-H	1	1	-C(=O)-
185	-$CH_2CH(CH_3)$	-H	-H	-H	1	1	-C(=O)-
186	-C(=O)CH_3	-H	-H	-H	1	1	-C(=O)-
187	-C(=O)CF_3	-H	-H	-H	1	1	-C(=O)-
188	-C(=O)OCH_3	-H	-H	-H	1	1	-C(=O)-
189	-C(=O)$OC(CH_3)_3$	-H	-H	-H	1	1	-C(=O)-
190	-$S(=O)_2CH_3$	-H	-H	-H	1	1	-C(=O)-
191		-H	-H	-H	1	1	-C(=O)-
192		-H	-H	-H	1	1	-C(=O)-
193		-H	-H	-H	1	1	-C(=O)-
194		-H	-H	-H	1	1	-C(=O)-
195		-H	-H	-H	1	1	-C(=O)-
196	-H	-H	-H	-F	1	1	-C(=O)-
197	-CH_3	-H	-H	-F	1	1	-C(=O)-
198	-CH_2CH_3	-H	-H	-F	1	1	-C(=O)-
199	-$CH(CH_3)$	-H	-H	-F	1	1	-C(=O)-
200	-$CH_2CH(CH_3)$	-H	-H	-F	1	1	-C(=O)-
201	-C(=O)CH_3	-H	-H	-F	1	1	-C(=O)-
202	-C(=O)CF_3	-H	-H	-F	1	1	-C(=O)-
203	-C(=O)OCH_3	-H	-H	-F	1	1	-C(=O)-
204	-C(=O)$OC(CH_3)_3$	-H	-H	-F	1	1	-C(=O)-
205	-$S(=O)_2CH_3$	-H	-H	-F	1	1	-C(=O)-
206		-H	-H	-F	1	1	-C(=O)-
207		-H	-H	-F	1	1	-C(=O)-
208		-H	-H	-F	1	1	-C(=O)-
209		-H	-H	-F	1	1	-C(=O)-
210		-H	-H	-F	1	1	-C(=O)-
211	-H	-H	-H	-CH_3	1	1	-C(=O)-
212	-CH_3	-H	-H	-CH_3	1	1	-C(=O)-
213	-CH_2CH_3	-H	-H	-CH_3	1	1	-C(=O)-
214	-$CH(CH_3)$	-H	-H	-CH_3	1	1	-C(=O)-
215	-$CH_2CH(CH_3)$	-H	-H	-CH_3	1	1	-C(=O)-
216	-C(=O)CH_3	-H	-H	-CH_3	1	1	-C(=O)-
217	-C(=O)CF_3	-H	-H	-CH_3	1	1	-C(=O)-

218	-C(=O)OCH_3	-H	-H	-CH_3	1	1	-C(=O)-
219	-C(=O)$OC(CH_3)_3$	-H	-H	-CH_3	1	1	-C(=O)-
220	-$S(=O)_2CH_3$	-H	-H	-CH_3	1	1	-C(=O)-
221		-H	-H	-CH_3	1	1	-C(=O)-
222		-H	-H	-CH_3	1	1	-C(=O)-
223		-H	-H	-CH_3	1	1	-C(=O)-
224		-H	-H	-CH_3	1	1	-C(=O)-
225		-H	-H	-CH_3	1	1	-C(=O)-
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227	-CH_3	-H	-H	-D	1	1	-C(=O)-
228	-CH_2CH_3	-H	-H	-D	1	1	-C(=O)-
229	-$CH(CH_3)$	-H	-H	-D	1	1	-C(=O)-
230	-$CH_2CH(CH_3)$	-H	-H	-D	1	1	-C(=O)-
231	-C(=O)CH_3	-H	-H	-D	1	1	-C(=O)-
232	-C(=O)CF_3	-H	-H	-D	1	1	-C(=O)-
233	-C(=O)OCH_3	-H	-H	-D	1	1	-C(=O)-
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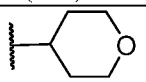
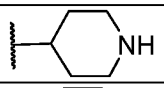
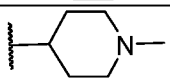
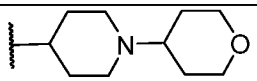
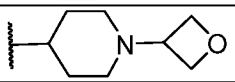
236		-H	-H	-D	1	1	-C(=O)-
237		-H	-H	-D	1	1	-C(=O)-
238		-H	-H	-D	1	1	-C(=O)-
239		-H	-H	-D	1	1	-C(=O)-
240		-H	-H	-D	1	1	-C(=O)-
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242	-CH_3	-H	-H	-H	2	1	-C(=O)-
243	-CH_2CH_3	-H	-H	-H	2	1	-C(=O)-
244	-$CH(CH_3)$	-H	-H	-H	2	1	-C(=O)-
245	-$CH_2CH(CH_3)$	-H	-H	-H	2	1	-C(=O)-
246	-C(=O)CH_3	-H	-H	-H	2	1	-C(=O)-
247	-C(=O)CF_3	-H	-H	-H	2	1	-C(=O)-
248	-C(=O)OCH_3	-H	-H	-H	2	1	-C(=O)-
249	-C(=O)$OC(CH_3)_3$	-H	-H	-H	2	1	-C(=O)-
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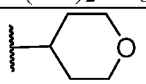
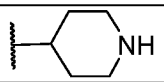
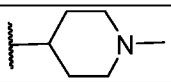
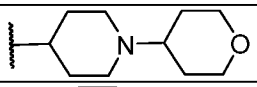
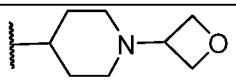
251		-H	-H	-H	2	1	-C(=O)-
252		-H	-H	-H	2	1	-C(=O)-

253		-H	-H	-H	2	1	-C(=O)-
254		-H	-H	-H	2	1	-C(=O)-
255		-H	-H	-H	2	1	-C(=O)-
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258	$-CH_2CH_3$	-H	-H	-F	2	1	-C(=O)-
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260	$-CH_2CH(CH_3)$	-H	-H	-F	2	1	-C(=O)-
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263	$-C(=O)OCH_3$	-H	-H	-F	2	1	-C(=O)-
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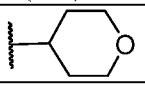
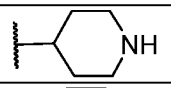
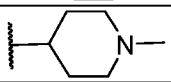
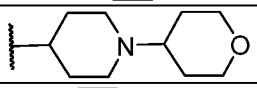
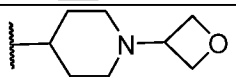
266		-H	-H	-F	2	1	-C(=O)-
267		-H	-H	-F	2	1	-C(=O)-
268		-H	-H	-F	2	1	-C(=O)-
269		-H	-H	-F	2	1	-C(=O)-
270		-H	-H	-F	2	1	-C(=O)-
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273	$-CH_2CH_3$	-H	-H	$-CH_3$	2	1	-C(=O)-
274	$-CH(CH_3)$	-H	-H	$-CH_3$	2	1	-C(=O)-
275	$-CH_2CH(CH_3)$	-H	-H	$-CH_3$	2	1	-C(=O)-
276	$-C(=O)CH_3$	-H	-H	$-CH_3$	2	1	-C(=O)-
277	$-C(=O)CF_3$	-H	-H	$-CH_3$	2	1	-C(=O)-
278	$-C(=O)OCH_3$	-H	-H	$-CH_3$	2	1	-C(=O)-
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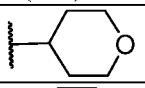
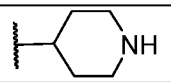
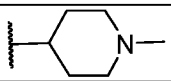
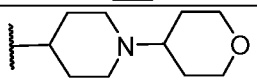
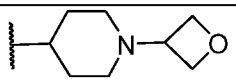
281		-H	-H	$-CH_3$	2	1	-C(=O)-
282		-H	-H	$-CH_3$	2	1	-C(=O)-
283		-H	-H	$-CH_3$	2	1	-C(=O)-
284		-H	-H	$-CH_3$	2	1	-C(=O)-
285		-H	-H	$-CH_3$	2	1	-C(=O)-
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287	$-CH_3$	-H	-H	-D	2	1	-C(=O)-

288	-CH_2CH_3	-H	-H	-D	2	1	-C(=O)-
289	-$CH(CH_3)$	-H	-H	-D	2	1	-C(=O)-
290	-$CH_2CH(CH_3)$	-H	-H	-D	2	1	-C(=O)-
291	-$C(=O)CH_3$	-H	-H	-D	2	1	-C(=O)-
292	-$C(=O)CF_3$	-H	-H	-D	2	1	-C(=O)-
293	-$C(=O)OCH_3$	-H	-H	-D	2	1	-C(=O)-
294	-$C(=O)OC(CH_3)_3$	-H	-H	-D	2	1	-C(=O)-
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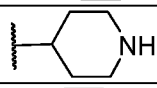
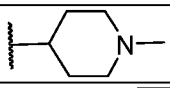
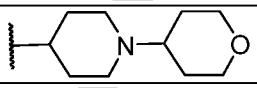
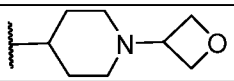
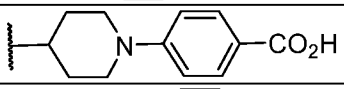
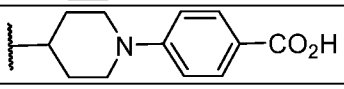
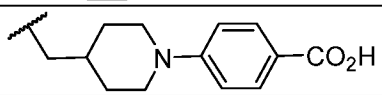
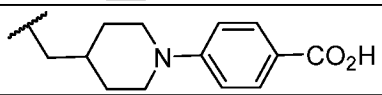
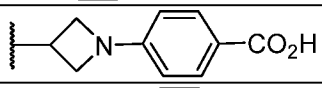
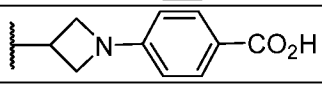
297		-H	-H	-D	2	1	-C(=O)-
298		-H	-H	-D	2	1	-C(=O)-
299		-H	-H	-D	2	1	-C(=O)-
300		-H	-H	-D	2	1	-C(=O)-
828		-H	-H	-H	1	1	-C(=O)-
829		-H	-H	-H	1	1	-CH_2-
830		-H	-H	-H	1	1	-C(=O)-
831		-H	-H	-H	1	1	-CH_2-
832		-H	-H	-H	1	1	-C(=O)-
833		-H	-H	-H	1	1	-CH_2-
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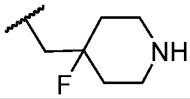
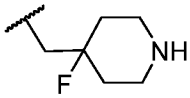
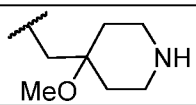
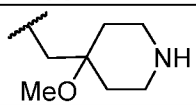
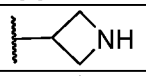
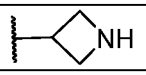
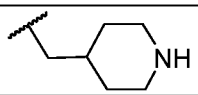
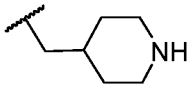
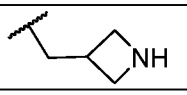
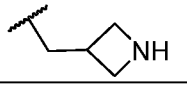
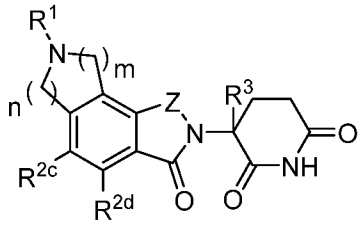
836		-H	-H	-H	1	1	-C(=O)-
837		-H	-H	-H	1	1	-CH_2-
838		-H	-H	-H	1	1	-C(=O)-
839		-H	-H	-H	1	1	-CH_2-
840		-H	-H	-H	1	1	-C(=O)-
841		-H	-H	-H	1	1	-CH_2-

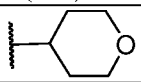
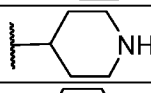
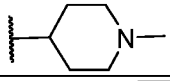
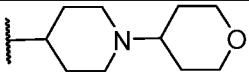
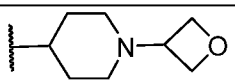
842		-H	-H	-H	1	1	-C(=O)-
843		-H	-H	-H	1	1	$-CH_2-$
842		-H	-H	-H	1	1	-C(=O)-
843		-H	-H	-H	1	1	$-CH_2-$
854	$-C(=O)OC(CH_3)_3$	-H	-H	-H	2	2	-C(=O)-
855	-H	-H	-H	-H	2	2	-C(=O)-
856	$-C(=O)OC(CH_3)_3$	-H	-H	-H	1	3	-C(=O)-
857	-H	-H	-H	-H	1	3	-C(=O)-

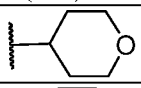
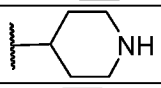
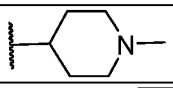
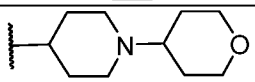
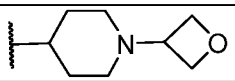
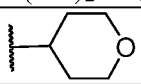
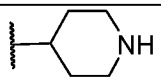
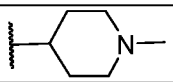
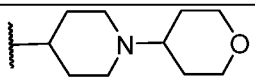
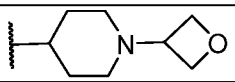
[0171] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, wherein R^1, R^{2c}, R^{2d}, R^3, m, n, and Z are as defined in Table 2, or a pharmaceutically acceptable salt or solvate thereof.

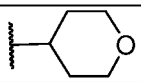
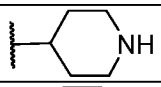
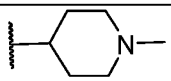
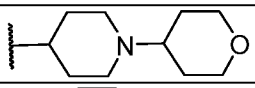
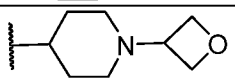
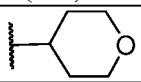
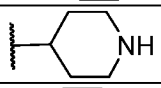
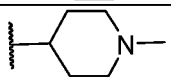
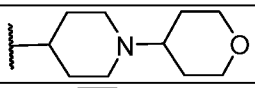
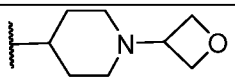
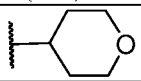
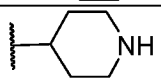
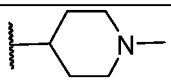
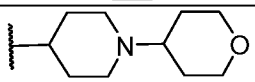
Table 2

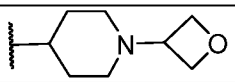
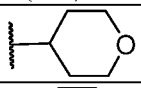
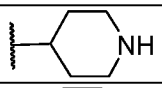
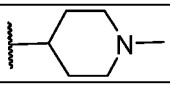
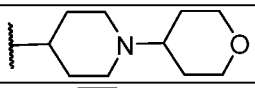
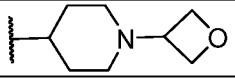


III

Cpd. No.	R^1	R^{2a}	R^{2d}	R^3	m	n	Z
301	-H	-H	-H	-H	1	1	$-CH_2-$
302	$-CH_3$	-H	-H	-H	1	1	$-CH_2-$
303	$-CH_2CH_3$	-H	-H	-H	1	1	$-CH_2-$
304	$-CH(CH_3)$	-H	-H	-H	1	1	$-CH_2-$
305	$-CH_2CH(CH_3)$	-H	-H	-H	1	1	$-CH_2-$
306	$-C(=O)CH_3$	-H	-H	-H	1	1	$-CH_2-$
307	$-C(=O)CF_3$	-H	-H	-H	1	1	$-CH_2-$
308	$-C(=O)OCH_3$	-H	-H	-H	1	1	$-CH_2-$
309	$-C(=O)OC(CH_3)_3$	-H	-H	-H	1	1	$-CH_2-$
310	$-S(=O)_2CH_3$	-H	-H	-H	1	1	$-CH_2-$
311		-H	-H	-H	1	1	$-CH_2-$
312		-H	-H	-H	1	1	$-CH_2-$
313		-H	-H	-H	1	1	$-CH_2-$
314		-H	-H	-H	1	1	$-CH_2-$
315		-H	-H	-H	1	1	$-CH_2-$
316	-H	-H	-H	-F	1	1	$-CH_2-$
317	$-CH_3$	-H	-H	-F	1	1	$-CH_2-$

318	$-CH_2CH_3$	-H	-H	-F	1	1	$-CH_2-$
319	$-CH(CH_3)$	-H	-H	-F	1	1	$-CH_2-$
320	$-CH_2CH(CH_3)$	-H	-H	-F	1	1	$-CH_2-$
321	$-C(=O)CH_3$	-H	-H	-F	1	1	$-CH_2-$
322	$-C(=O)CF_3$	-H	-H	-F	1	1	$-CH_2-$
323	$-C(=O)OCH_3$	-H	-H	-F	1	1	$-CH_2-$
324	$-C(=O)OC(CH_3)_3$	-H	-H	-F	1	1	$-CH_2-$
325	$-S(=O)_2CH_3$	-H	-H	-F	1	1	$-CH_2-$
326		-H	-H	-F	1	1	$-CH_2-$
327		-H	-H	-F	1	1	$-CH_2-$
328		-H	-H	-F	1	1	$-CH_2-$
329		-H	-H	-F	1	1	$-CH_2-$
330		-H	-H	-F	1	1	$-CH_2-$
331	-H	-H	-H	$-CH_3$	1	1	$-CH_2-$
332	$-CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
333	$-CH_2CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
334	$-CH(CH_3)$	-H	-H	$-CH_3$	1	1	$-CH_2-$
335	$-CH_2CH(CH_3)$	-H	-H	$-CH_3$	1	1	$-CH_2-$
336	$-C(=O)CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
337	$-C(=O)CF_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
338	$-C(=O)OCH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
339	$-C(=O)OC(CH_3)_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
340	$-S(=O)_2CH_3$	-H	-H	$-CH_3$	1	1	$-CH_2-$
341		-H	-H	$-CH_3$	1	1	$-CH_2-$
342		-H	-H	$-CH_3$	1	1	$-CH_2-$
343		-H	-H	$-CH_3$	1	1	$-CH_2-$
344		-H	-H	$-CH_3$	1	1	$-CH_2-$
345		-H	-H	$-CH_3$	1	1	$-CH_2-$
346	-H	-H	-H	-D	1	1	$-CH_2-$
347	$-CH_3$	-H	-H	-D	1	1	$-CH_2-$
348	$-CH_2CH_3$	-H	-H	-D	1	1	$-CH_2-$
349	$-CH(CH_3)$	-H	-H	-D	1	1	$-CH_2-$
350	$-CH_2CH(CH_3)$	-H	-H	-D	1	1	$-CH_2-$
351	$-C(=O)CH_3$	-H	-H	-D	1	1	$-CH_2-$
352	$-C(=O)CF_3$	-H	-H	-D	1	1	$-CH_2-$
353	$-C(=O)OCH_3$	-H	-H	-D	1	1	$-CH_2-$
354	$-C(=O)OC(CH_3)_3$	-H	-H	-D	1	1	$-CH_2-$
355	$-S(=O)_2CH_3$	-H	-H	-D	1	1	$-CH_2-$

356		-H	-H	-D	1	1	-CH_2-
357		-H	-H	-D	1	1	-CH_2-
358		-H	-H	-D	1	1	-CH_2-
359		-H	-H	-D	1	1	-CH_2-
360		-H	-H	-D	1	1	-CH_2-
361	-H	-H	-H	-H	2	1	-CH_2-
362	-CH_3	-H	-H	-H	2	1	-CH_2-
363	-CH_2CH_3	-H	-H	-H	2	1	-CH_2-
364	-$CH(CH_3)$	-H	-H	-H	2	1	-CH_2-
365	-$CH_2CH(CH_3)$	-H	-H	-H	2	1	-CH_2-
366	-$C(=O)CH_3$	-H	-H	-H	2	1	-CH_2-
367	-$C(=O)CF_3$	-H	-H	-H	2	1	-CH_2-
368	-$C(=O)OCH_3$	-H	-H	-H	2	1	-CH_2-
369	-$C(=O)OC(CH_3)_3$	-H	-H	-H	2	1	-CH_2-
370	-$S(=O)_2CH_3$	-H	-H	-H	2	1	-CH_2-
371		-H	-H	-H	2	1	-CH_2-
372		-H	-H	-H	2	1	-CH_2-
373		-H	-H	-H	2	1	-CH_2-
374		-H	-H	-H	2	1	-CH_2-
375		-H	-H	-H	2	1	-CH_2-
376	-H	-H	-H	-F	2	1	-CH_2-
377	-CH_3	-H	-H	-F	2	1	-CH_2-
378	-CH_2CH_3	-H	-H	-F	2	1	-CH_2-
379	-$CH(CH_3)$	-H	-H	-F	2	1	-CH_2-
380	-$CH_2CH(CH_3)$	-H	-H	-F	2	1	-CH_2-
381	-$C(=O)CH_3$	-H	-H	-F	2	1	-CH_2-
382	-$C(=O)CF_3$	-H	-H	-F	2	1	-CH_2-
383	-$C(=O)OCH_3$	-H	-H	-F	2	1	-CH_2-
384	-$C(=O)OC(CH_3)_3$	-H	-H	-F	2	1	-CH_2-
385	-$S(=O)_2CH_3$	-H	-H	-F	2	1	-CH_2-
386		-H	-H	-F	2	1	-CH_2-
387		-H	-H	-F	2	1	-CH_2-
388		-H	-H	-F	2	1	-CH_2-
389		-H	-H	-F	2	1	-CH_2-

390		-H	-H	-F	2	1	-CH_2-
391	-H	-H	-H	-CH_3	2	1	-CH_2-
392	-CH_3	-H	-H	-CH_3	2	1	-CH_2-
393	-CH_2CH_3	-H	-H	-CH_3	2	1	-CH_2-
394	-$CH(CH_3)$	-H	-H	-CH_3	2	1	-CH_2-
395	-$CH_2CH(CH_3)$	-H	-H	-CH_3	2	1	-CH_2-
396	-$C(=O)CH_3$	-H	-H	-CH_3	2	1	-CH_2-
397	-$C(=O)CF_3$	-H	-H	-CH_3	2	1	-CH_2-
398	-$C(=O)OCH_3$	-H	-H	-CH_3	2	1	-CH_2-
399	-$C(=O)OC(CH_3)_3$	-H	-H	-CH_3	2	1	-CH_2-
400	-$S(=O)_2CH_3$	-H	-H	-CH_3	2	1	-CH_2-
401		-H	-H	-CH_3	2	1	-CH_2-
402		-H	-H	-CH_3	2	1	-CH_2-
403		-H	-H	-CH_3	2	1	-CH_2-
404		-H	-H	-CH_3	2	1	-CH_2-
405		-H	-H	-CH_3	2	1	-CH_2-
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408	-CH_2CH_3	-H	-H	-D	2	1	-CH_2-
409	-$CH(CH_3)$	-H	-H	-D	2	1	-CH_2-
410	-$CH_2CH(CH_3)$	-H	-H	-D	2	1	-CH_2-
411	-$C(=O)CH_3$	-H	-H	-D	2	1	-CH_2-
412	-$C(=O)CF_3$	-H	-H	-D	2	1	-CH_2-
413	-$C(=O)OCH_3$	-H	-H	-D	2	1	-CH_2-
414	-$C(=O)OC(CH_3)_3$	-H	-H	-D	2	1	-CH_2-
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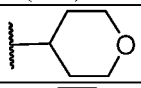
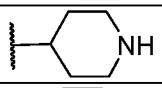
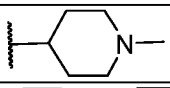
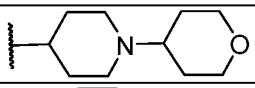
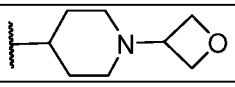
416		-H	-H	-D	2	1	-CH_2-
417		-H	-H	-D	2	1	-CH_2-
418		-H	-H	-D	2	1	-CH_2-
419		-H	-H	-D	2	1	-CH_2-
420		-H	-H	-D	2	1	-CH_2-
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423	-CH_2CH_3	-H	-H	-H	1	2	-CH_2-
424	-$CH(CH_3)$	-H	-H	-H	1	2	-CH_2-
425	-$CH_2CH(CH_3)$	-H	-H	-H	1	2	-CH_2-
426	-$C(=O)CH_3$	-H	-H	-H	1	2	-CH_2-
427	-$C(=O)CF_3$	-H	-H	-H	1	2	-CH_2-

428	-C(=O)OCH_3	-H	-H	-H	1	2	-CH_2-
429	-C(=O)$OC(CH_3)_3$	-H	-H	-H	1	2	-CH_2-
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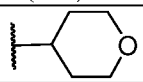
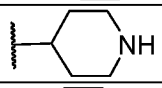
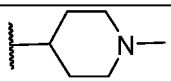
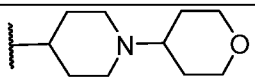
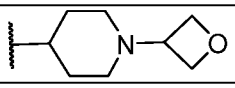
431		-H	-H	-H	1	2	-CH_2-
432		-H	-H	-H	1	2	-CH_2-
433		-H	-H	-H	1	2	-CH_2-
434		-H	-H	-H	1	2	-CH_2-
435		-H	-H	-H	1	2	-CH_2-
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438	-CH_2CH_3	-H	-H	-F	1	2	-CH_2-
439	-$CH(CH_3)$	-H	-H	-F	1	2	-CH_2-
440	-$CH_2CH(CH_3)$	-H	-H	-F	1	2	-CH_2-
441	-C(=O)CH_3	-H	-H	-F	1	2	-CH_2-
442	-C(=O)CF_3	-H	-H	-F	1	2	-CH_2-
443	-C(=O)OCH_3	-H	-H	-F	1	2	-CH_2-
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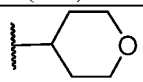
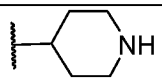
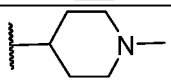
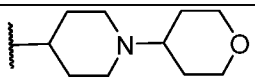
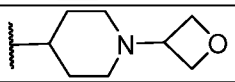
446		-H	-H	-F	1	2	-CH_2-
447		-H	-H	-F	1	2	-CH_2-
448		-H	-H	-F	1	2	-CH_2-
449		-H	-H	-F	1	2	-CH_2-
450		-H	-H	-F	1	2	-CH_2-
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453	-CH_2CH_3	-H	-H	-CH_3	1	2	-CH_2-
454	-$CH(CH_3)$	-H	-H	-CH_3	1	2	-CH_2-
455	-$CH_2CH(CH_3)$	-H	-H	-CH_3	1	2	-CH_2-
456	-C(=O)CH_3	-H	-H	-CH_3	1	2	-CH_2-
457	-C(=O)CF_3	-H	-H	-CH_3	1	2	-CH_2-
458	-C(=O)OCH_3	-H	-H	-CH_3	1	2	-CH_2-
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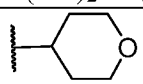
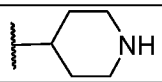
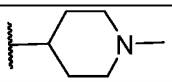
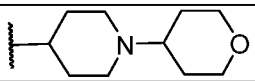
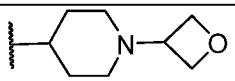
461		-H	-H	-CH_3	1	2	-CH_2-
462		-H	-H	-CH_3	1	2	-CH_2-

463		-H	-H	$-CH_3$	1	2	$-CH_2-$
464		-H	-H	$-CH_3$	1	2	$-CH_2-$
465		-H	-H	$-CH_3$	1	2	$-CH_2-$
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467	$-CH_3$	-H	-H	-D	1	2	$-CH_2-$
468	$-CH_2CH_3$	-H	-H	-D	1	2	$-CH_2-$
469	$-CH(CH_3)$	-H	-H	-D	1	2	$-CH_2-$
470	$-CH_2CH(CH_3)$	-H	-H	-D	1	2	$-CH_2-$
471	$-C(=O)CH_3$	-H	-H	-D	1	2	$-CH_2-$
472	$-C(=O)CF_3$	-H	-H	-D	1	2	$-CH_2-$
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474	$-C(=O)OC(CH_3)_3$	-H	-H	-D	1	2	$-CH_2-$
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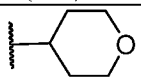
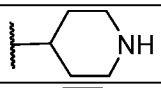
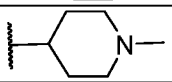
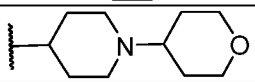
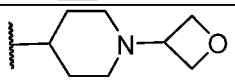
476		-H	-H	-D	1	2	$-CH_2-$
477		-H	-H	-D	1	2	$-CH_2-$
478		-H	-H	-D	1	2	$-CH_2-$
479		-H	-H	-D	1	2	$-CH_2-$
480		-H	-H	-D	1	2	$-CH_2-$
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487	$-C(=O)CF_3$	-H	-H	-H	1	1	-C(=O)-
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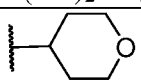
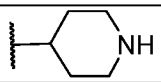
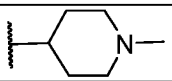
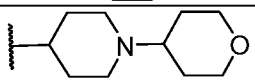
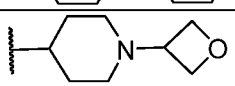
491		-H	-H	-H	1	1	-C(=O)-
492		-H	-H	-H	1	1	-C(=O)-
493		-H	-H	-H	1	1	-C(=O)-
494		-H	-H	-H	1	1	-C(=O)-
495		-H	-H	-H	1	1	-C(=O)-
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497	$-CH_3$	-H	-H	-F	1	1	-C(=O)-

498	-CH_2CH_3	-H	-H	-F	1	1	-C(=O)-
499	-$CH(CH_3)$	-H	-H	-F	1	1	-C(=O)-
500	-$CH_2CH(CH_3)$	-H	-H	-F	1	1	-C(=O)-
501	-$C(=O)CH_3$	-H	-H	-F	1	1	-C(=O)-
502	-$C(=O)CF_3$	-H	-H	-F	1	1	-C(=O)-
503	-$C(=O)OCH_3$	-H	-H	-F	1	1	-C(=O)-
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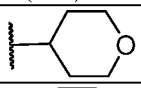
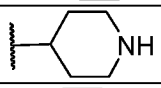
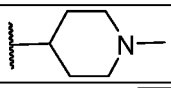
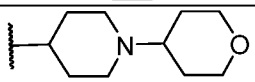
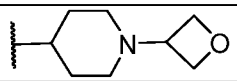
506		-H	-H	-F	1	1	-C(=O)-
507		-H	-H	-F	1	1	-C(=O)-
508		-H	-H	-F	1	1	-C(=O)-
509		-H	-H	-F	1	1	-C(=O)-
510		-H	-H	-F	1	1	-C(=O)-
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516	-$C(=O)CH_3$	-H	-H	-CH_3	1	1	-C(=O)-
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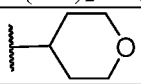
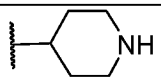
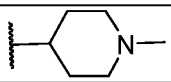
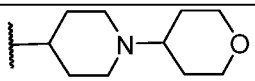
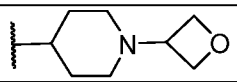
521		-H	-H	-CH_3	1	1	-C(=O)-
522		-H	-H	-CH_3	1	1	-C(=O)-
523		-H	-H	-CH_3	1	1	-C(=O)-
524		-H	-H	-CH_3	1	1	-C(=O)-
525		-H	-H	-CH_3	1	1	-C(=O)-
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528	-CH_2CH_3	-H	-H	-D	1	1	-C(=O)-
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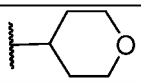
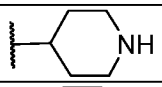
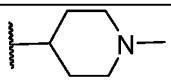
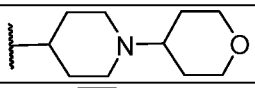
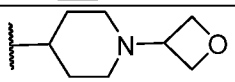
536		-H	-H	-D	1	1	-C(=O)-
537		-H	-H	-D	1	1	-C(=O)-
538		-H	-H	-D	1	1	-C(=O)-
539		-H	-H	-D	1	1	-C(=O)-
540		-H	-H	-D	1	1	-C(=O)-
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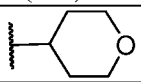
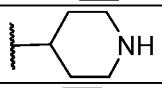
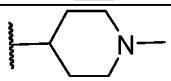
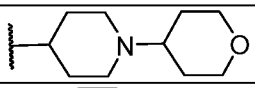
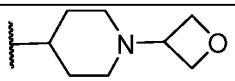
551		-H	-H	-H	2	1	-C(=O)-
552		-H	-H	-H	2	1	-C(=O)-
553		-H	-H	-H	2	1	-C(=O)-
554		-H	-H	-H	2	1	-C(=O)-
555		-H	-H	-H	2	1	-C(=O)-
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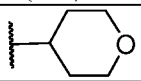
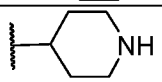
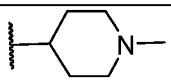
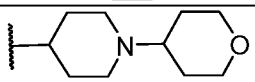
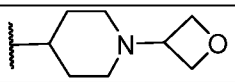
566		-H	-H	-F	2	1	-C(=O)-
567		-H	-H	-F	2	1	-C(=O)-
568		-H	-H	-F	2	1	-C(=O)-
569		-H	-H	-F	2	1	-C(=O)-

570		-H	-H	-F	2	1	-C(=O)-
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576	$-C(=O)CH_3$	-H	-H	$-CH_3$	2	1	-C(=O)-
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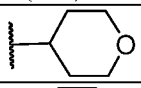
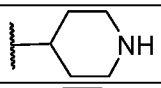
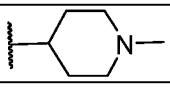
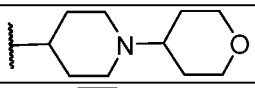
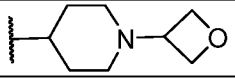
581		-H	-H	$-CH_3$	2	1	-C(=O)-
582		-H	-H	$-CH_3$	2	1	-C(=O)-
583		-H	-H	$-CH_3$	2	1	-C(=O)-
584		-H	-H	$-CH_3$	2	1	-C(=O)-
585		-H	-H	$-CH_3$	2	1	-C(=O)-
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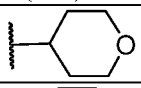
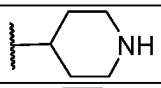
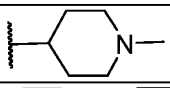
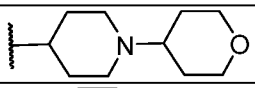
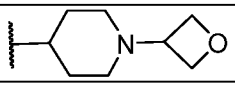
596		-H	-H	-D	2	1	-C(=O)-
597		-H	-H	-D	2	1	-C(=O)-
598		-H	-H	-D	2	1	-C(=O)-
599		-H	-H	-D	2	1	-C(=O)-
600		-H	-H	-D	2	1	-C(=O)-
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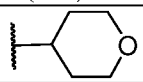
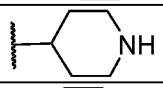
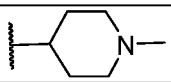
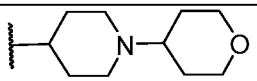
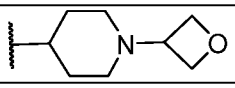
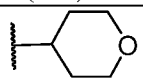
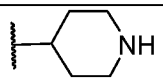
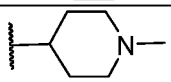
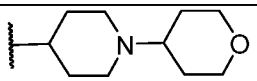
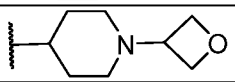
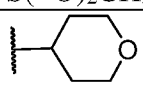
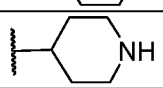
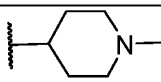
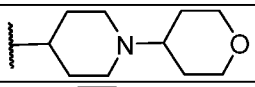
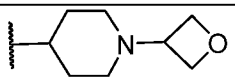
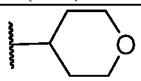
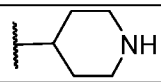
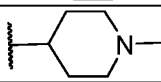
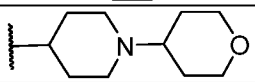
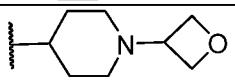
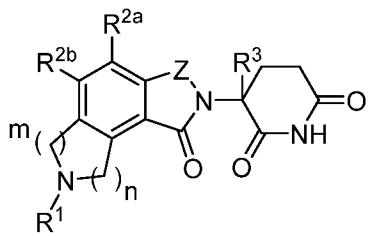
611		-H	-H	-H	1	2	-C(=O)-
612		-H	-H	-H	1	2	-C(=O)-
613		-H	-H	-H	1	2	-C(=O)-
614		-H	-H	-H	1	2	-C(=O)-
615		-H	-H	-H	1	2	-C(=O)-
616	-H	-H	-H	-F	1	2	-C(=O)-
617	-CH_3	-H	-H	-F	1	2	-C(=O)-
618	-CH_2CH_3	-H	-H	-F	1	2	-C(=O)-
619	-$CH(CH_3)$	-H	-H	-F	1	2	-C(=O)-
620	-$CH_2CH(CH_3)$	-H	-H	-F	1	2	-C(=O)-
621	-C(=O)CH_3	-H	-H	-F	1	2	-C(=O)-
622	-C(=O)CF_3	-H	-H	-F	1	2	-C(=O)-
623	-C(=O)OCH_3	-H	-H	-F	1	2	-C(=O)-
624	-C(=O)$OC(CH_3)_3$	-H	-H	-F	1	2	-C(=O)-
625	-$S(=O)_2CH_3$	-H	-H	-F	1	2	-C(=O)-
626		-H	-H	-F	1	2	-C(=O)-
627		-H	-H	-F	1	2	-C(=O)-
628		-H	-H	-F	1	2	-C(=O)-
629		-H	-H	-F	1	2	-C(=O)-
630		-H	-H	-F	1	2	-C(=O)-
631	-H	-H	-H	-CH_3	1	2	-C(=O)-
632	-CH_3	-H	-H	-CH_3	1	2	-C(=O)-
633	-CH_2CH_3	-H	-H	-CH_3	1	2	-C(=O)-
634	-$CH(CH_3)$	-H	-H	-CH_3	1	2	-C(=O)-
635	-$CH_2CH(CH_3)$	-H	-H	-CH_3	1	2	-C(=O)-
636	-C(=O)CH_3	-H	-H	-CH_3	1	2	-C(=O)-
637	-C(=O)CF_3	-H	-H	-CH_3	1	2	-C(=O)-
638	-C(=O)OCH_3	-H	-H	-CH_3	1	2	-C(=O)-
639	-C(=O)$OC(CH_3)_3$	-H	-H	-CH_3	1	2	-C(=O)-
640	-$S(=O)_2CH_3$	-H	-H	-CH_3	1	2	-C(=O)-
641		-H	-H	-CH_3	1	2	-C(=O)-
642		-H	-H	-CH_3	1	2	-C(=O)-

643		-H	-H	$-CH_3$	1	2	-C(=O)-
644		-H	-H	$-CH_3$	1	2	-C(=O)-
645		-H	-H	$-CH_3$	1	2	-C(=O)-
631	-H	-H	-H	-D	1	2	-C(=O)-
632	$-CH_3$	-H	-H	-D	1	2	-C(=O)-
633	$-CH_2CH_3$	-H	-H	-D	1	2	-C(=O)-
634	$-CH(CH_3)$	-H	-H	-D	1	2	-C(=O)-
635	$-CH_2CH(CH_3)$	-H	-H	-D	1	2	-C(=O)-
636	$-C(=O)CH_3$	-H	-H	-D	1	2	-C(=O)-
637	$-C(=O)CF_3$	-H	-H	-D	1	2	-C(=O)-
638	$-C(=O)OCH_3$	-H	-H	-D	1	2	-C(=O)-
639	$-C(=O)OC(CH_3)_3$	-H	-H	-D	1	2	-C(=O)-
640	$-S(=O)_2CH_3$	-H	-H	-D	1	2	-C(=O)-
641		-H	-H	-D	1	2	-C(=O)-
642		-H	-H	-D	1	2	-C(=O)-
643		-H	-H	-D	1	2	-C(=O)-
644		-H	-H	-D	1	2	-C(=O)-
645		-H	-H	-D	1	2	-C(=O)-
858	-H	-H	-H	-H	3	1	-C(=O)-
859	-H	-H	-H	-H	2	2	-C(=O)-

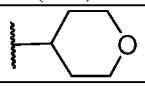
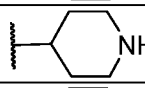
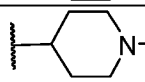
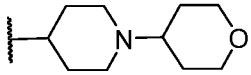
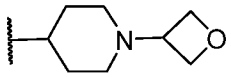
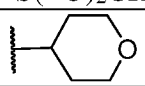
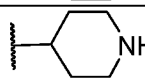
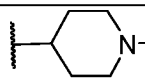
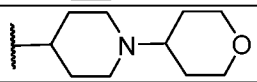
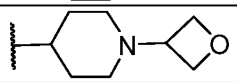
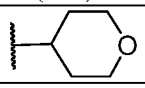
[0172] In another embodiment, Compounds of the Disclosure are compounds of Formula **IV**, wherein R^1, R^{2a}, R^{2b}, R^3, m, n, and Z are as defined in Table 3, or a pharmaceutically acceptable salt or solvate thereof.

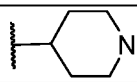
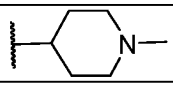
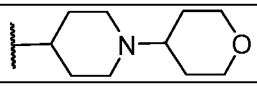
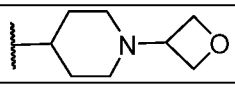
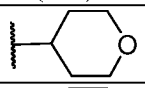
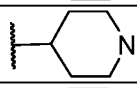
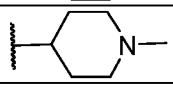
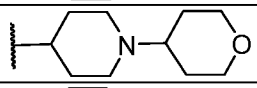
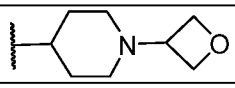
Table 3



IV

Cpd. No.	R^1	R^{2a}	R^{2d}	R^3	m	n	Z
646	-H	-H	-H	-H	1	1	$-CH_2-$
647	$-CH_3$	-H	-H	-H	1	1	$-CH_2-$
648	$-CH_2CH_3$	-H	-H	-H	1	1	$-CH_2-$
649	$-CH(CH_3)$	-H	-H	-H	1	1	$-CH_2-$
650	$-CH_2CH(CH_3)$	-H	-H	-H	1	1	$-CH_2-$

651	-C(=O)CH_3	-H	-H	-H	1	1	-CH_2-
652	-C(=O)CF_3	-H	-H	-H	1	1	-CH_2-
653	-C(=O)OCH_3	-H	-H	-H	1	1	-CH_2-
654	-C(=O)$OC(CH_3)_3$	-H	-H	-H	1	1	-CH_2-
655	-$S(=O)_2CH_3$	-H	-H	-H	1	1	-CH_2-
656		-H	-H	-H	1	1	-CH_2-
657		-H	-H	-H	1	1	-CH_2-
658		-H	-H	-H	1	1	-CH_2-
659		-H	-H	-H	1	1	-CH_2-
660		-H	-H	-H	1	1	-CH_2-
661	-H	-H	-H	-F	1	1	-CH_2-
662	-CH_3	-H	-H	-F	1	1	-CH_2-
663	-CH_2CH_3	-H	-H	-F	1	1	-CH_2-
664	-$CH(CH_3)$	-H	-H	-F	1	1	-CH_2-
665	-$CH_2CH(CH_3)$	-H	-H	-F	1	1	-CH_2-
666	-C(=O)CH_3	-H	-H	-F	1	1	-CH_2-
667	-C(=O)CF_3	-H	-H	-F	1	1	-CH_2-
668	-C(=O)OCH_3	-H	-H	-F	1	1	-CH_2-
669	-C(=O)$OC(CH_3)_3$	-H	-H	-F	1	1	-CH_2-
670	-$S(=O)_2CH_3$	-H	-H	-F	1	1	-CH_2-
671		-H	-H	-F	1	1	-CH_2-
672		-H	-H	-F	1	1	-CH_2-
673		-H	-H	-F	1	1	-CH_2-
674		-H	-H	-F	1	1	-CH_2-
675		-H	-H	-F	1	1	-CH_2-
676	-H	-H	-H	-CH_3	1	1	-CH_2-
677	-CH_3	-H	-H	-CH_3	1	1	-CH_2-
678	-CH_2CH_3	-H	-H	-CH_3	1	1	-CH_2-
679	-$CH(CH_3)$	-H	-H	-CH_3	1	1	-CH_2-
680	-$CH_2CH(CH_3)$	-H	-H	-CH_3	1	1	-CH_2-
681	-C(=O)CH_3	-H	-H	-CH_3	1	1	-CH_2-
682	-C(=O)CF_3	-H	-H	-CH_3	1	1	-CH_2-
683	-C(=O)OCH_3	-H	-H	-CH_3	1	1	-CH_2-
684	-C(=O)$OC(CH_3)_3$	-H	-H	-CH_3	1	1	-CH_2-
685	-$S(=O)_2CH_3$	-H	-H	-CH_3	1	1	-CH_2-
686		-H	-H	-CH_3	1	1	-CH_2-

687		-H	-H	$-CH_3$	1	1	$-CH_2-$
688		-H	-H	$-CH_3$	1	1	$-CH_2-$
689		-H	-H	$-CH_3$	1	1	$-CH_2-$
690		-H	-H	$-CH_3$	1	1	$-CH_2-$
691	-H	-H	-H	-D	1	1	$-CH_2-$
692	$-CH_3$	-H	-H	-D	1	1	$-CH_2-$
693	$-CH_2CH_3$	-H	-H	-D	1	1	$-CH_2-$
694	$-CH(CH_3)$	-H	-H	-D	1	1	$-CH_2-$
695	$-CH_2CH(CH_3)$	-H	-H	-D	1	1	$-CH_2-$
696	$-C(=O)CH_3$	-H	-H	-D	1	1	$-CH_2-$
697	$-C(=O)CF_3$	-H	-H	-D	1	1	$-CH_2-$
698	$-C(=O)OCH_3$	-H	-H	-D	1	1	$-CH_2-$
699	$-C(=O)OC(CH_3)_3$	-H	-H	-D	1	1	$-CH_2-$
700	$-S(=O)_2CH_3$	-H	-H	-D	1	1	$-CH_2-$
701		-H	-H	-D	1	1	$-CH_2-$
702		-H	-H	-D	1	1	$-CH_2-$
703		-H	-H	-D	1	1	$-CH_2-$
704		-H	-H	-D	1	1	$-CH_2-$
705		-H	-H	-D	1	1	$-CH_2-$
706	-H	-H	-H	-H	2	1	$-CH_2-$
707	$-CH_3$	-H	-H	-H	2	1	$-CH_2-$
708	$-CH_2CH_3$	-H	-H	-H	2	1	$-CH_2-$
709	$-CH(CH_3)$	-H	-H	-H	2	1	$-CH_2-$
710	$-CH_2CH(CH_3)$	-H	-H	-H	2	1	$-CH_2-$
711	$-C(=O)CH_3$	-H	-H	-H	2	1	$-CH_2-$
712	$-C(=O)CF_3$	-H	-H	-H	2	1	$-CH_2-$
713	$-C(=O)OCH_3$	-H	-H	-H	2	1	$-CH_2-$
714	$-C(=O)OC(CH_3)_3$	-H	-H	-H	2	1	$-CH_2-$
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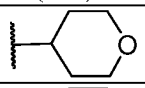
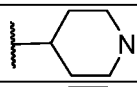
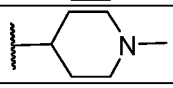
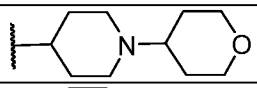
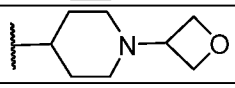
716		-H	-H	-H	2	1	$-CH_2-$
717		-H	-H	-H	2	1	$-CH_2-$
718		-H	-H	-H	2	1	$-CH_2-$
719		-H	-H	-H	2	1	$-CH_2-$
720		-H	-H	-H	2	1	$-CH_2-$

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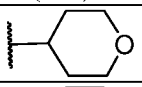
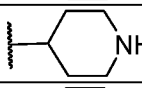
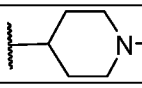
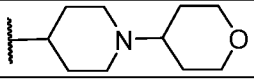
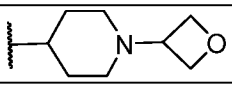
722	$-CH_3$	-H	-H	-F	2	1	$-CH_2-$
723	$-CH_2CH_3$	-H	-H	-F	2	1	$-CH_2-$
724	$-CH(CH_3)$	-H	-H	-F	2	1	$-CH_2-$
725	$-CH_2CH(CH_3)$	-H	-H	-F	2	1	$-CH_2-$
726	$-C(=O)CH_3$	-H	-H	-F	2	1	$-CH_2-$
727	$-C(=O)CF_3$	-H	-H	-F	2	1	$-CH_2-$
728	$-C(=O)OCH_3$	-H	-H	-F	2	1	$-CH_2-$
729	$-C(=O)OC(CH_3)_3$	-H	-H	-F	2	1	$-CH_2-$
730	$-S(=O)_2CH_3$	-H	-H	-F	2	1	$-CH_2-$
731		-H	-H	-F	2	1	$-CH_2-$
732		-H	-H	-F	2	1	$-CH_2-$
733		-H	-H	-F	2	1	$-CH_2-$
734		-H	-H	-F	2	1	$-CH_2-$
735		-H	-H	-F	2	1	$-CH_2-$
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737	$-CH_3$	-H	-H	$-CH_3$	2	1	$-CH_2-$
738	$-CH_2CH_3$	-H	-H	$-CH_3$	2	1	$-CH_2-$
739	$-CH(CH_3)$	-H	-H	$-CH_3$	2	1	$-CH_2-$
740	$-CH_2CH(CH_3)$	-H	-H	$-CH_3$	2	1	$-CH_2-$
741	$-C(=O)CH_3$	-H	-H	$-CH_3$	2	1	$-CH_2-$
742	$-C(=O)CF_3$	-H	-H	$-CH_3$	2	1	$-CH_2-$
743	$-C(=O)OCH_3$	-H	-H	$-CH_3$	2	1	$-CH_2-$
744	$-C(=O)OC(CH_3)_3$	-H	-H	$-CH_3$	2	1	$-CH_2-$
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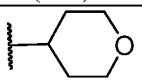
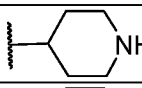
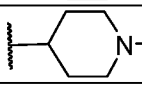
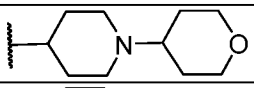
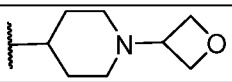
746		-H	-H	$-CH_3$	2	1	$-CH_2-$
747		-H	-H	$-CH_3$	2	1	$-CH_2-$
748		-H	-H	$-CH_3$	2	1	$-CH_2-$
749		-H	-H	$-CH_3$	2	1	$-CH_2-$
750		-H	-H	$-CH_3$	2	1	$-CH_2-$
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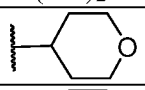
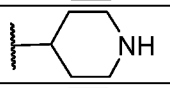
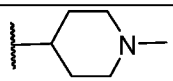
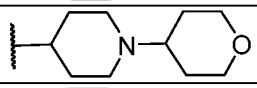
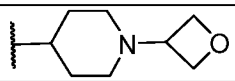
752	$-CH_3$	-H	-H	-D	2	1	$-CH_2-$
753	$-CH_2CH_3$	-H	-H	-D	2	1	$-CH_2-$
754	$-CH(CH_3)$	-H	-H	-D	2	1	$-CH_2-$
755	$-CH_2CH(CH_3)$	-H	-H	-D	2	1	$-CH_2-$
756	$-C(=O)CH_3$	-H	-H	-D	2	1	$-CH_2-$
757	$-C(=O)CF_3$	-H	-H	-D	2	1	$-CH_2-$
758	$-C(=O)OCH_3$	-H	-H	-D	2	1	$-CH_2-$
759	$-C(=O)OC(CH_3)_3$	-H	-H	-D	2	1	$-CH_2-$

760	-S(=O)$_2$CH$_3$	-H	-H	-D	2	1	-CH$_2$-
761		-H	-H	-D	2	1	-CH$_2$-
762		-H	-H	-D	2	1	-CH$_2$-
763		-H	-H	-D	2	1	-CH$_2$-
764		-H	-H	-D	2	1	-CH$_2$-
765		-H	-H	-D	2	1	-CH$_2$-
766	-H	-H	-H	-H	1	2	-CH$_2$-
767	-CH$_3$	-H	-H	-H	1	2	-CH$_2$-
768	-CH$_2$CH$_3$	-H	-H	-H	1	2	-CH$_2$-
769	-CH(CH$_3$)	-H	-H	-H	1	2	-CH$_2$-
770	-CH$_2$CH(CH$_3$)	-H	-H	-H	1	2	-CH$_2$-
771	-C(=O)CH$_3$	-H	-H	-H	1	2	-CH$_2$-
772	-C(=O)CF$_3$	-H	-H	-H	1	2	-CH$_2$-
773	-C(=O)OCH$_3$	-H	-H	-H	1	2	-CH$_2$-
774	-C(=O)OC(CH$_3$)$_3$	-H	-H	-H	1	2	-CH$_2$-
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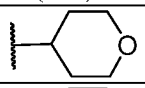
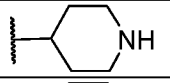
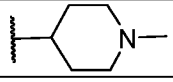
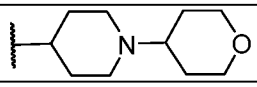
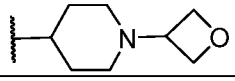
776		-H	-H	-H	1	2	-CH$_2$-
777		-H	-H	-H	1	2	-CH$_2$-
778		-H	-H	-H	1	2	-CH$_2$-
779		-H	-H	-H	1	2	-CH$_2$-
780		-H	-H	-H	1	2	-CH$_2$-
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782	-CH$_3$	-H	-H	-F	1	2	-CH$_2$-
783	-CH$_2$CH$_3$	-H	-H	-F	1	2	-CH$_2$-
784	-CH(CH$_3$)	-H	-H	-F	1	2	-CH$_2$-
785	-CH$_2$CH(CH$_3$)	-H	-H	-F	1	2	-CH$_2$-
786	-C(=O)CH$_3$	-H	-H	-F	1	2	-CH$_2$-
787	-C(=O)CF$_3$	-H	-H	-F	1	2	-CH$_2$-
788	-C(=O)OCH$_3$	-H	-H	-F	1	2	-CH$_2$-
789	-C(=O)OC(CH$_3$)$_3$	-H	-H	-F	1	2	-CH$_2$-
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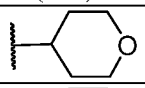
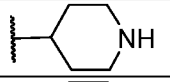
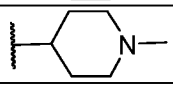
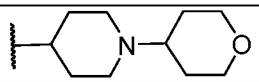
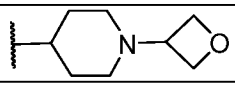
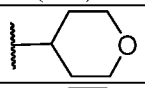
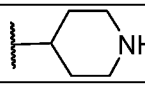
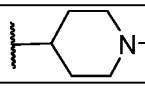
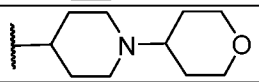
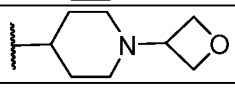
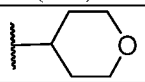
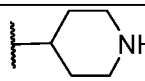
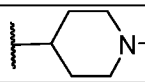
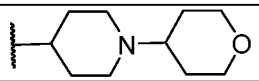
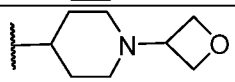
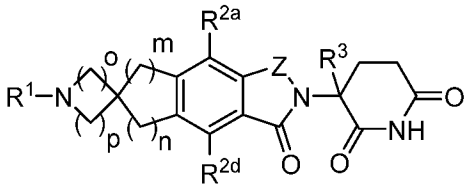
791		-H	-H	-F	1	2	-CH$_2$-
792		-H	-H	-F	1	2	-CH$_2$-
793		-H	-H	-F	1	2	-CH$_2$-

794		-H	-H	-F	1	2	-CH_2-
795		-H	-H	-F	1	2	-CH_2-
796	-H	-H	-H	-CH_3	1	2	-CH_2-
797	-CH_3	-H	-H	-CH_3	1	2	-CH_2-
798	-CH_2CH_3	-H	-H	-CH_3	1	2	-CH_2-
799	-$CH(CH_3)$	-H	-H	-CH_3	1	2	-CH_2-
800	-$CH_2CH(CH_3)$	-H	-H	-CH_3	1	2	-CH_2-
801	-$C(=O)CH_3$	-H	-H	-CH_3	1	2	-CH_2-
802	-$C(=O)CF_3$	-H	-H	-CH_3	1	2	-CH_2-
803	-$C(=O)OCH_3$	-H	-H	-CH_3	1	2	-CH_2-
804	-$C(=O)OC(CH_3)_3$	-H	-H	-CH_3	1	2	-CH_2-
805	-$S(=O)_2CH_3$	-H	-H	-CH_3	1	2	-CH_2-
806		-H	-H	-CH_3	1	2	-CH_2-
807		-H	-H	-CH_3	1	2	-CH_2-
808		-H	-H	-CH_3	1	2	-CH_2-
809		-H	-H	-CH_3	1	2	-CH_2-
810		-H	-H	-CH_3	1	2	-CH_2-
811	-H	-H	-H	-D	1	2	-CH_2-
812	-CH_3	-H	-H	-D	1	2	-CH_2-
813	-CH_2CH_3	-H	-H	-D	1	2	-CH_2-
814	-$CH(CH_3)$	-H	-H	-D	1	2	-CH_2-
815	-$CH_2CH(CH_3)$	-H	-H	-D	1	2	-CH_2-
816	-$C(=O)CH_3$	-H	-H	-D	1	2	-CH_2-
817	-$C(=O)CF_3$	-H	-H	-D	1	2	-CH_2-
818	-$C(=O)OCH_3$	-H	-H	-D	1	2	-CH_2-
819	-$C(=O)OC(CH_3)_3$	-H	-H	-D	1	2	-CH_2-
820	-$S(=O)_2CH_3$	-H	-H	-D	1	2	-CH_2-
821		-H	-H	-D	1	2	-CH_2-
822		-H	-H	-D	1	2	-CH_2-
823		-H	-H	-D	1	2	-CH_2-
824		-H	-H	-D	1	2	-CH_2-
825		-H	-H	-D	1	2	-CH_2-

[0173] In another embodiment, Compounds of the Disclosure are compounds of Formula **IX**, wherein R^1, R^{2a}, R^{2b}, R^3, m, n, o, p, and Z are as defined in Table 7, or a pharmaceutically acceptable salt or solvate thereof.

Table 7

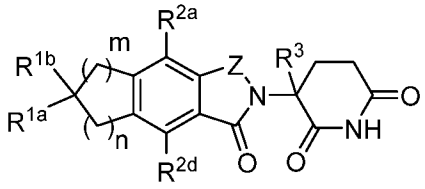


IX,

Cpd. No.	R^1	R^{2a}	R^{2d}	R^3	m	n	o	p	Z
826	-H	-H	-H	-H	1	1	1	1	$-CH_2-$
827	-H	-H	-H	-H	1	1	1	1	-C(=O)-
826a	-H	-H	-H	-H	1	1	2	2	$-CH_2-$
827a	-H	-H	-H	-H	1	1	2	2	-C(=O)-
860	-H	-H	-H	-H	1	1	1	2	-C(=O)-
861	-H	-H	-H	-H	1	1	2	3	-C(=O)-

[0174] In another embodiment, Compounds of the Disclosure are compounds of Formula **XIV**, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, m, n, and Z are as defined in Table 8, or a pharmaceutically acceptable salt or solvate thereof.

Table 8



XIV,

Cpd. No.	R^{1a}	R^{1b}	R^{2a}	R^{2d}	R^3	m	n	Z
844	-OH	-H	-H	-H	-H	1	1	$-CH_2-$
845	$-CH_2OH$	-H	-H	-H	-H	1	1	$-CH_2-$
846	-CHO	-H	-H	-H	-H	1	1	$-CH_2-$
847	-C(=O)OH	-H	-H	-H	-H	1	1	$-CH_2-$
848	-C(=O)-		-H	-H	-H	1	1	$-CH_2-$
849	-OH	-H	-H	-H	-H	1	1	-C(=O)-
850	$-CH_2OH$	-H	-H	-H	-H	1	1	-C(=O)-
851	-CHO	-H	-H	-H	-H	1	1	-C(=O)-
852	-C(=O)OH	-H	-H	-H	-H	1	1	-C(=O)-
853	-C(=O)-		-H	-H	-H	1	1	-C(=O)-

[0175] The present disclosure encompasses the preparation and use of salts of Compounds of the Disclosure. As used herein, the pharmaceutical "pharmaceutically acceptable salt" refers to salts or zwitterionic forms of Compounds of the Disclosure. Salts of Compounds of the Disclosure can be prepared during the final isolation and purification of the compounds or separately by reacting the compound with a suitable acid. The pharmaceutically acceptable salts of Compounds of the Disclosure can be acid

addition salts formed with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Non-limiting examples of salts of compounds of the disclosure include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulfonate, and p-toluenesulfonate salts. In addition, available amino groups present in the compounds of the disclosure can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. In light of the foregoing, any reference Compounds of the Disclosure appearing herein is intended to include compounds of Compounds of the Disclosure as well as pharmaceutically acceptable salts, hydrates, or solvates thereof.

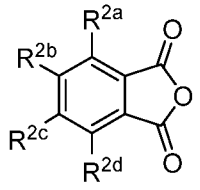
[0176] The present disclosure encompasses the preparation and use of solvates of Compounds of the Disclosure. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of the present disclosure with a solvent molecule such as, e.g. a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound of the present disclosure is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of the Disclosure can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, and ethanol, and it is

intended that the disclosure includes both solvated and unsolvated forms of Compounds of the Disclosure. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a Compound of the Disclosure in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, e.g., filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvate in a crystal of the solvate.

II. Intermediates of the Disclosure

[0177] The disclosure also provides synthetic intermediates, collectively referred to as "Intermediates of the Disclosure," that can be used to prepare Compounds of the Disclosure.

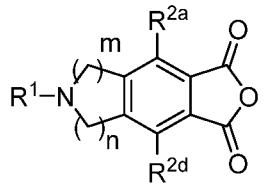
[0178] In one embodiment, Intermediates of the Disclosure are compounds of Formula **VI**:



VI,

wherein R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$; and R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^4, R^5, R^6, and R^7 are as defined in connection with Formula **I**.

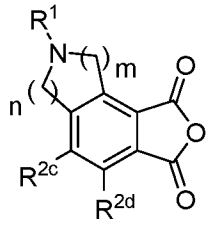
[0179] In another embodiment, Intermediates of the Disclosure are compounds of Formula **VII**:



VII,

wherein R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$; and R^{2a}, R^{2d}, m, n, R^4, R^5, R^6, and R^7 are as defined in connection with Formula **II**.

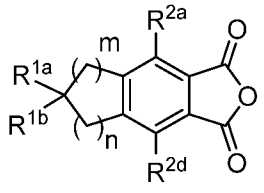
[0180] In another embodiment, Intermediates of the Disclosure are compounds of of Formula **VIII**:



VIII,

wherein R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$; and R^{2c}, R^{2d}, m, n, R^4, R^5, R^6, and R^7 are as defined in connection with Formula **III**.

[0181] In another embodiment, Intermediates of the Disclosure are compounds of Formula **XVII**:



XVII

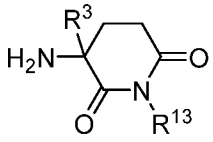
wherein R^{1a}, R^{1b}, R^{2a}, R^{2d}, R^3, m, and n are as defined in connection with Formula **XIV**.

III. Methods of Preparing Compounds of the Disclosure

[0182] The disclosure also provides methods of preparing Compounds of the Disclosure.

[0183] In one embodiment, the disclosure provides a method of making a compound of Formula **I**, wherein Z is -C(=O)-, the method comprising:

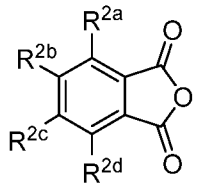
[0184] (i) reacting a compound of Formula **V**:



V,

or a salt, e.g., HCl salt, thereof, wherein R^3 is as defined in connection with Formula **I**;

[0185] with compound of Formula **VI**:

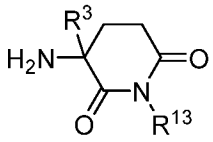


VI,

[0186] in a solvent, wherein R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)R^4, -S(=O)$_2R^5$, and -C(=NR^6)R^7; and R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^4, R^5, R^6, and R^7 are as defined in connection with Formula **I**.

[0187] In another embodiment, the disclosure provides a method of making a compound of Formula **II**, wherein Z is -C(=O)-, the method comprising:

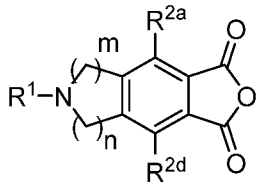
[0188] (i) reacting a compound of Formula **V**:



V,

or a salt, e.g., HCl salt, thereof, wherein R^3 is as defined in connection with Formula **I**;

[0189] with compound of Formula **VII**:



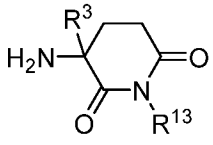
VII,

[0190] in a solvent, wherein R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-

C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)R^4, -S(=O)$_2R^5$, and -C(=NR^6)R^7; and R^{2a}, R^{2d} , m, n, R^4, R^5, R^6, and R^7 are as defined in connection with Formula **II**.

[0191] In another embodiment, the disclosure provides a method of making a compound of Formula **III**, wherein Z is -C(=O)-, the method comprising:

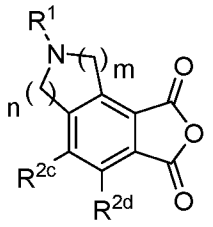
[0192] (i) reacting a compound of Formula **V**:



V,

or a salt, e.g., HCl salt, thereof, wherein R^3 is as defined in connection with Formula **I**;

[0193] with compound of Formula **VIII**:



VIII,

[0194] in a solvent, wherein R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)R^4, -S(=O)$_2R^5$, and -C(=NR^6)R^7; and R^{2c}, R^{2d} , m, n, R^4, R^5, R^6, and R^7 are as defined in connection with Formula **III**.

[0195] In another embodiment, R^1 is -C(=O)R^4 and R^4 is -OR^{4b}. In another embodiment, R^{4b} is C_1-C_4 alkyl.

[0196] In another embodiment, the solvent is selected from the group consisting of toluene, benzene, xylene, tetrahydrofuran (THF), dioxane, dimethylformamide (DMF), dimethylacetamide (DMA), N-methyl-2-pyrrolidone (NMP), dimethylsulfoxide (DMSO), acetic acid, and acetonitrile.

[0197] In another embodiment, Formula **V** is reacted with Formula **VI** at a temperature of about 40 °C to about 150 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 40 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 50 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 60 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 70 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 80 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 90 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 100 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 110 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 120 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 130 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 140 °C. In another embodiment, Formula **V** is reacted with Formula **VI** at about 150 °C.

IV. Methods of Treating Disease with Compounds of the Disclosure and PROTAC Molecules

[0198] Compounds of the Disclosure inhibit CRBN ubiquitination and are thus useful in the treatment or prevention of a variety of diseases and conditions. In particular, Compounds of the Disclosure are useful in methods of treating or preventing a disease or condition wherein inhibition of CRBN ubiquitination provides a benefit. Foremost among these diseases and conditions are cancers and proliferative diseases. In one embodiment, such a cancer is referred to as a "CRBN-mediated cancer." CRBN-mediated cancers are known in the art. The therapeutic methods of this disclosure comprise administering a therapeutically effective amount of a Compound of the Disclosure to a subject, e.g., human, in need thereof. The present methods also encompass optionally administering an optional therapeutic agent to the subject in addition to the Compound of the Disclosure. The optional therapeutic agent is selected from drugs known as useful in treating the disease or condition afflicting the subject in need thereof, e.g., a chemotherapeutic agent and/or radiation known as useful in treating a particular cancer.

[0199] In another embodiment, the present disclosure relates to a method of treating an individual suffering from a disease or condition wherein inhibition of CRBN

ubiquitination provides a benefit, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure.

[0200] Since Compounds of the Disclosure inhibit CRBN ubiquitination, a number of diseases and conditions mediated by CRBN ubiquitination can be treated by employing these compounds. The present disclosure is thus directed generally to a method for treating a condition or disorder responsive to inhibition of CRBN ubiquitination in a subject, e.g., a human subject, suffering from, or at risk of suffering from, a condition or disorder, e.g., cancer or inflammatory disease, the method comprising administering to the subject an effective amount of one or more Compounds of the Disclosure.

[0201] In another embodiment, the present disclosure is directed to a method of inhibiting CRBN ubiquitination in a subject in need thereof, said method comprising administering to the subject an effective amount of at least one Compound of the Disclosure.

[0202] The methods of the present disclosure can be accomplished by administering a Compound of the Disclosure or PROTAC Molecule as the neat compound or as a pharmaceutical composition. Administration of a pharmaceutical composition, or neat compound of a Compound of the Disclosure or PROTAC Molecule, can be performed during or after the onset of the disease or condition of interest. Typically, the pharmaceutical compositions are sterile, and contain no toxic, carcinogenic, or mutagenic compounds that would cause an adverse reaction when administered. Further provided are kits comprising a Compound of the Disclosure and, optionally, an optional therapeutic agent, packaged separately or together, and an insert having instructions for using these active agents.

[0203] In one embodiment, a Compound of the Disclosure is administered in conjunction with an optional therapeutic agent useful in the treatment of a disease or condition wherein inhibition of CRBN ubiquitination provides a benefit. The optional therapeutic agent is different from the Compound of the Disclosure. A Compound of the Disclosure and the optional therapeutic agent can be administered simultaneously or sequentially to achieve the desired effect. In addition, the Compound of the Disclosure and optional therapeutic agent can be administered from a single composition or two separate compositions. Likewise, in another embodiment, a PROTAC Molecule is administered in conjunction with an optional therapeutic agent.

[0204] The optional therapeutic agent is administered in an amount to provide its desired therapeutic effect. The effective dosage range for each optional therapeutic agent is

known in the art, and the optional therapeutic agent is administered to an individual in need thereof within such established ranges.

[0205] A Compound of the Disclosure or PROTAC Molecule and the optional therapeutic agent can be administered together as a single-unit dose or separately as multi-unit doses, wherein the Compound of the Disclosure or PROTAC Molecule is administered before the optional therapeutic agent or vice versa. One or more doses of the Compound of the Disclosure and/or one or more dose of the optional therapeutic agent can be administered. The Compound of the Disclosure or PROTAC Molecule therefore can be used in conjunction with one or more optional therapeutic agents, for example, but not limited to, anticancer agents.

[0206] Diseases and conditions treatable by the methods of the present disclosure include, but are not limited to, cancer and other proliferative disorders, or an inflammatory disease. In one embodiment, a human subject is treated with a Compound of the Disclosure, or a pharmaceutical composition comprising a Compound of the Disclosure, wherein the compound is administered in an amount sufficient to inhibit CRBN ubiquitination in the subject.

[0207] In another aspect, the present disclosure provides a method of treating cancer in a subject comprising administering a therapeutically effective amount of a Compound of the Disclosure. While not being limited to a specific mechanism, in some embodiments, Compounds of the Disclosure treat cancer by inhibiting CRBN ubiquitination.

[0208] In another aspect, the present disclosure provides a method of treating cancer in a subject comprising administering a therapeutically effective amount of a PROTAC Molecule to the subject.

[0209] Examples of treatable cancers include, but are not limited to, any one or more of the cancers of Table 4.

Table 4

adrenal cancer	acinic cell carcinoma	acoustic neuroma	acral lentigious 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 myelogeous 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	preimary peritoneal cancer
prostate cancer	pancreatic cancer	pharyngeal cancer	pseudomyxoma periotonei
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
Wilms' tumor			

[0210] In another embodiment, the cancer is a solid tumor. In another embodiment, the cancer a hematological cancer. Exemplary hematological cancers include, but are not limited to, the cancers listed in Table 5. In another embodiment, the hematological

cancer is acute lymphocytic leukemia, chronic lymphocytic leukemia (including B-cell chronic lymphocytic leukemia), or acute myeloid leukemia. In another embodiment, the hematological cancer is multiple myeloma.

Table 5

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 myelogeous 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
Richter's transformation	

[0211] In another embodiment, the cancer is a leukemia, for example a leukemia selected from acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia and mixed lineage leukemia (MLL). In another embodiment the cancer is NUT-midline carcinoma. In another embodiment the cancer is multiple myeloma. In another embodiment the cancer is a lung cancer such as small cell lung cancer (SCLC). In another embodiment the cancer is a neuroblastoma. In another embodiment the cancer is Burkitt's lymphoma. In another embodiment the cancer is cervical cancer. In another embodiment the cancer is esophageal cancer. In another embodiment the cancer is ovarian cancer. In another embodiment the cancer is colorectal cancer. In another embodiment, the cancer is prostate cancer. In another embodiment, the cancer is breast cancer.

[0212] In another embodiment, the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal

cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

[0213] In another embodiment, the present disclosure provides a method of treating a benign proliferative disorder, such as, but are not limited to, benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, meningioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseudotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord nodules, polyps, and cysts, Castleman disease, chronic pilonidal disease, dermatofibroma, pilar cyst, pyogenic granuloma, and juvenile polyposis syndrome.

[0214] In another embodiment, the present disclosure provides a method of treating an inflammatory disease. For example, Compounds of the Disclosure can be used to treat infectious and noninfectious inflammatory events and autoimmune and other inflammatory diseases by administration of a therapeutically effective amount to a subject, in particular a human in need of such treatment. Examples of autoimmune and inflammatory diseases, disorders, and syndromes treated using the compounds and methods described herein include inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholocystitus, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, Type I diabetes, septic shock, lupus, e.g., cutaneous lupus, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituatarism, Guillain-Barre syndrome, Behcet's disease, scleracierma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[0215] In another embodiment, the present disclosure provides a therapeutic method of modulating CRBN ubiquitination *in vivo* in diseases mentioned above, in particular cancer, by administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such therapy.

[0216] In methods of the present disclosure, a therapeutically effective amount of a Compound of the Disclosure or PROTAC Molecule, typically formulated in accordance with pharmaceutical practice, is administered to a human being in need thereof. Whether such a treatment is indicated depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[0217] A Compound of the Disclosure or PROTAC Molecule can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration. Parenteral administration can be accomplished using a needle and syringe or using a high pressure technique.

[0218] Pharmaceutical compositions include those wherein a Compound of the Disclosure or PROTAC Molecule is administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of a Compound of the Disclosure or PROTAC Molecule that is sufficient to maintain therapeutic effects.

[0219] Toxicity and therapeutic efficacy of the Compounds of the Disclosure or the PROTAC Molecules can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in animals. The dose ratio between the maximum tolerated dose and therapeutic effects (e.g. inhibiting of tumor growth) is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration

utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0220] A therapeutically effective amount of a Compound of the Disclosure or PROTAC Molecule required for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the subject, and ultimately is determined by the attendant physician. Dosage amounts and intervals can be adjusted individually to provide plasma levels of the Compound of the Disclosure that are sufficient to maintain the desired therapeutic effects. The desired dose can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day. Multiple doses often are desired, or required. For example, a Compound of the Disclosure can be administered at a frequency of: four doses delivered as one dose per day at four-day intervals (q4d x 4); four doses delivered as one dose per day at three-day intervals (q3d x 4); one dose delivered per day at five-day intervals (qd x 5); one dose per week for three weeks (qwk3); five daily doses, with two days rest, and another five daily doses (5/2/5); or, any dose regimen determined to be appropriate for the circumstance.

[0221] A Compound of the Disclosure or PROTAC Molecule used in a method of the present disclosure can be administered in an amount of about 0.005 to about 500 milligrams per dose, about 0.05 to about 250 milligrams per dose, or about 0.5 to about 100 milligrams per dose. For example, a Compound of the Disclosure or PROTAC Molecule can be administered, per dose, in an amount of about 0.005, about 0.05, about 0.5, about 5, about 10, about 20, about 30, about 40, about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 milligrams, including all doses between 0.005 and 500 milligrams.

[0222] The dosage of a composition containing a Compound of the Disclosure or PROTAC Molecule, or a composition containing the same, can be from about 1 ng/kg to about 200 mg/kg, about 1 μg/kg to about 100 mg/kg, or about 1 mg/kg to about 50 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, about 1 μg/kg. The dosage of a composition may be at any dosage including, but not limited to, about 1 μg/kg, about 10 μg/kg, about 25 μg/kg, about 50 μg/kg, about 75 μg/kg, about 100 μg/kg, about 125 μg/kg, about 150 μg/kg, about 175 μg/kg, about 200 μg/kg, about 225 μg/kg, about 250 μg/kg, about 275 μg/kg, about 300 μg/kg, about 325 μg/kg, about 350 μg/kg, about 375 μg/kg, about 400 μg/kg, about 425 μg/kg, about 450 μg/kg, about 475 μg/kg, about 500 μg/kg, about 525 μg/kg, about 550 μg/kg, about

575 μg/kg, about 600 μg/kg, about 625 μg/kg, about 650 μg/kg, about 675 μg/kg, about 700 μg/kg, about 725 μg/kg, about 750 μg/kg, about 775 μg/kg, about 800 μg/kg, about 825 μg/kg, about 850 μg/kg, about 875 μg/kg, about 900 μg/kg, about 925 μg/kg, about 950 μg/kg, about 975 μg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, or more. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines the actual dosing regimen that is most suitable for an individual subject, which can vary with the age, weight, and response of the particular subject.

[0223] Compounds of the Disclosure and PROTAC Molecules typically are administered in admixture with a pharmaceutical carrier to give a pharmaceutical composition selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present disclosure are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of Compound of the Disclosure or PROTAC Molecule.

[0224] These pharmaceutical compositions can be manufactured, for example, by conventional mixing, dissolving, granulating, dragee-making, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of the Compound of the Disclosure is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition additionally can contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 0.01% to about 95%, and preferably from about 1% to about 50%, of a Compound of the Disclosure or PROTAC Molecule. When administered in liquid form, a liquid carrier, such as water, petroleum, or oils of animal or plant origin, can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.1% to about 90%, and preferably about 1% to about 50%, by weight, of a Compound of the Disclosure or PROTAC Molecule.

[0225] When a therapeutically effective amount of a Compound of the Disclosure or PROTAC Molecule is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, an isotonic vehicle.

[0226] Compounds of the Disclosure or PROTAC Molecules can be readily combined with pharmaceutically acceptable carriers well-known in the art. Standard pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995. Such carriers enable the active agents to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained by adding the Compound of the Disclosure to a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

[0227] Compounds of the Disclosure or PROTAC Molecules can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[0228] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active agent in water-soluble form. Additionally, suspensions of a Compound of the Disclosure or PROTAC Molecule can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0229] Compounds of the Disclosure or PROTAC Molecules also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the Compound of the Disclosure also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the Compound of the Disclosure can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins.

[0230] In particular, the Compounds of the Disclosure or PROTAC Molecules can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. Compounds of the Disclosure or PROTAC Molecules also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the Compounds of the Disclosure or PROTAC Molecules are typically used in the form of a sterile aqueous solution which can contain other substances, for example, salts or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

V. Optional Therapeutic Agents

[0231] In some therapeutic methods and uses of the disclosure, a Compound of the Disclosure or PROTAC Molecule is administered to a subject having a disease, disorder, or condition, e.g., cancer, as a single agent. In other therapeutic methods and uses of the disclosure, a Compound of the Disclosure or PROTAC Molecule is administered to a subject having a disease, disorder, or condition, e.g., cancer, in combination with one or more optional therapeutic agents. In one embodiment, a Compound of the Disclosure or PROTAC Molecule is administered in combination with one optional therapeutic agent. In another embodiment, a Compound of the Disclosure or PROTAC Molecule is administered in combination with two optional therapeutic agents. In another embodiment, a Compound of the Disclosure or PROTAC Molecule is administered in combination with three optional therapeutic agents. Optional therapeutic agents useful in treating cancer patients include those known in the art as well as those developed in the future.

[0232] Optional therapeutic agents are administered in an amount to provide their desired therapeutic effect. The effective dosage range for each optional therapeutic agent is known in the art, and the optional therapeutic agent is administered to an individual in need thereof within such established ranges.

[0233] A Compound of the Disclosure or PROTAC Molecule and the optional therapeutic agent(s) can be administered together as a single-unit dose or separately as multi-unit doses, and in any order, e.g., wherein a Compound of the Disclosure is administered before the optional therapeutic agent(s), or vice versa. One or more doses of a Compound of the Disclosure or PROTAC Molecule and the optional therapeutic agent(s) can be administered to the subject.

[0234] In one embodiment, the optional therapeutic agent is an immune checkpoint inhibitor. Immune checkpoint inhibitors are therapies that blockade immune system inhibitor checkpoints. Immune checkpoints can be stimulatory or inhibitory. Blockade of inhibitory immune checkpoint activates immune system function and can be used for cancer immunotherapy. Pardoll, *Nature Reviews. Cancer 12:*252-64 (2012). Tumor cells turn off activated T cells when they attach to specific T-cell receptors. Immune checkpoint inhibitors prevent tumor cells from attaching to T cells, which results in T cells remaining activated. In effect, the coordinated action by cellular and soluble components combats pathogens and injuries by cancers. The modulation of immune system pathways may involve changing the expression or the functional activity of at least one component of the pathway to then modulate the response by the immune system. U.S. 2015/0250853. Examples of immune checkpoint inhibitors include PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, LAG3 inhibitors, TIM3 inhibitors, cd47 inhibitors, and B7-H1 inhibitors. Thus, in one embodiment, the immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, and a cd47 inhibitor.

[0235] In another embodiment, the immune checkpoint inhibitor is a programmed cell death (PD-1) inhibitor. PD-1 is a T-cell coinhibitory receptor that plays a pivotal role in the ability of tumor cells to evade the host's immune system. Blockage of interactions between PD-1 and PD-L1, a ligand of PD-1, enhances immune function and mediates antitumor activity. Examples of PD-1 inhibitors include antibodies that specifically bind to PD-1. Particular anti-PD-1 antibodies include, but are not limited to nivolumab, pembrolizumab, STI-A1014, pidilzumab, and cemiplimab-rwlc. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies of

anti-PD-1 antibodies, see U.S. 2013/0309250, U.S. 6,808,710, U.S. 7,595,048, U.S. 8,008,449, U.S. 8,728,474, U.S. 8,779,105, U.S. 8,952,136, U.S. 8,900,587, U.S. 9,073,994, U.S. 9,084,776, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0236] In another embodiment, the immune checkpoint inhibitor is a PD-L1 (also known as B7-H1 or CD274) inhibitor. Examples of PD-L1 inhibitors include antibodies that specifically bind to PD-L1. Particular anti-PD-L1 antibodies include, but are not limited to, avelumab, atezolizumab, durvalumab, and BMS-936559. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 8,217,149, U.S. 2014/0341917, U.S. 2013/0071403, WO 2015036499, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0237] In another embodiment, the immune checkpoint inhibitor is a CTLA-4 inhibitor. CTLA-4, also known as cytotoxic T-lymphocyte antigen 4, is a protein receptor that downregulates the immune system. CTLA-4 is characterized as a "brake" that binds costimulatory molecules on antigen-presenting cells, which prevents interaction with CD28 on T cells and also generates an overtly inhibitory signal that constrains T cell activation. Examples of CTLA-4 inhibitors include antibodies that specifically bind to CTLA-4. Particular anti-CTLA-4 antibodies include, but are not limited to, ipilimumab and tremelimumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 6,984,720, U.S. 6,207,156, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0238] In another embodiment, the immune checkpoint inhibitor is a LAG3 inhibitor. LAG3, Lymphocyte Activation Gene 3, is a negative co-simulatory receptor that modulates T cell homeostatis, proliferation, and activation. In addition, LAG3 has been reported to participate in regulatory T cells (Tregs) suppressive function. A large proportion of LAG3 molecules are retained in the cell close to the microtubule-organizing center, and only induced following antigen specific T cell activation. U.S. 2014/0286935. Examples of LAG3 inhibitors include antibodies that specifically bind to LAG3. Particular anti-LAG3 antibodies include, but are not limited to, GSK2831781. For a general discussion of the availability, methods of production, mechanism of action, and studies, see, U.S. 2011/0150892, U.S. 2014/0093511, U.S. 20150259420, and Huang *et al.*, *Immunity* 21:503-13 (2004).

[0239] In another embodiment, the immune checkpoint inhibitor is a TIM3 inhibitor. TIM3, T-cell immunoglobulin and mucin domain 3, is an immune checkpoint receptor

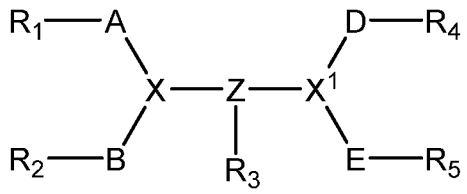
that functions to limit the duration and magnitude of T_H1 and T_C1 T-cell responses. The TIM3 pathway is considered a target for anticancer immunotherapy due to its expression on dysfunctional $CD8^+$ T cells and Tregs, which are two reported immune cell populations that constitute immunosuppression in tumor tissue. Anderson, *Cancer Immunology Research 2:*393-98 (2014). Examples of TIM3 inhibitors include antibodies that specifically bind to TIM3. For a general discussion of the availability, methods of production, mechanism of action, and studies of TIM3 inhibitors, see U.S. 20150225457, U.S. 20130022623, U.S. 8,522,156, Ngiow *et al.*, *Cancer Res 71:* 6567-71 (2011), Ngiow, *et al.*, *Cancer Res 71:*3540-51 (2011), and *Anderson*, *Cancer Immunology Res* 2:393-98 (2014).

[0240] In another embodiment, the immune checkpoint inhibitor is a cd47 inhibitor. *See* Unanue, E.R., *PNAS* 110:10886-87 (2013).

[0241] The term "antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity. In another embodiment, "antibody" is meant to include soluble receptors that do not possess the Fc portion of the antibody. In one embodiment, the antibodies are humanized monoclonal antibodies and fragments thereof made by means of recombinant genetic engineering.

[0242] Another class of immune checkpoint inhibitors include polypeptides that bind to and block PD-1 receptors on T-cells without triggering inhibitor signal transduction. Such peptides include B7-DC polypeptides, B7-H1 polypeptides, B7-1 polypeptides and B7-2 polypeptides, and soluble fragments thereof, as disclosed in U.S. Pat. 8,114,845.

[0243] Another class of immune checkpoint inhibitors include compounds with peptide moieties that inhibit PD-1 signaling. Examples of such compounds are disclosed in U.S. Pat. 8,907,053 and have the structure:



or a pharmaceutically acceptable salt thereof, wherein the compound comprises at least 5 amino acids useful as therapeutic agents capable of inhibiting the PD-1 signaling pathway.

[0244] Another class of immune checkpoint inhibitors include inhibitors of certain metabolic enzymes, such as indoleamine 2,3 dioxygenase (IDO), which is expressed by infiltrating myeloid cells and tumor cells, and isocitrate dehydrogenase (IDH), which is mutated in leukemia cells. Mutants of the IDH enzyme lead to increased levels of 2-hydroxyglutarate (2-HG), which prevent myeloid differentiation. Stein *et al.*, *Blood 130:*722-31 (2017); Wouters, *Blood 130:*693-94 (2017). Particular mutant IDH blocking agents include, but are not limited to, ivosidenib and enasidenib mesylate. Dalle and DiNardo, *Ther Adv Hematol 9(7):*163-73 (2018); Nassereddine *et al.*, *Onco Targets Ther 12:*303-08 (2018). The IDO enzyme inhibits immune responses by depleting amino acids that are necessary for anabolic functions in T cells or through the synthesis of particular natural ligands for cytosolic receptors that are able to alter lymphocyte functions. Pardoll, *Nature Reviews. Cancer 12:*252-64 (2012); Löb, *Cancer Immunol Immunother 58:*153-57 (2009). Particular IDO blocking agents include, but are not limited to, levo-1-methyl typtophan (L-1MT) and 1-methyl-tryptophan (1MT). Qian *et al., Cancer Res 69:*5498-504 (2009); and Löb *et al., Cancer Immunol Immunother 58:*153-7 (2009).

[0245] In one embodiment, the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, STI-A1110, avelumab, atezolizumab, durvalumab, STI-A1014, ipilimumab, tremelimumab, GSK2831781, BMS-936559 or MED14736.

[0246] In another embodiment, the optional therapeutic agent is an epigenetic drug. As used herein, the term "epigenetic drug" refers to a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, but are not limited to, vorinostat and panobinostat lactate.

[0247] In another embodiment, the optional therapeutic agent is a chemotherapeutic agent or other anti-proliferative agent that can be administered in combination with a Compound of the Disclosure to treat cancer. Examples of conventional therapies and anticancer agents that can be used in combination with a Compound of the Disclosure include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF), hyperthermia and cryotherapy, an agent to attenuate any adverse effect (e.g., an antiemetic), and any other approved biologic therapy or chemotherapy, e.g., a treatment regimen that uses drugs to stop the growth of

cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated.

[0248] Nonlimiting exemplary antiproliferative compounds include an aromatase inhibitor; an anti-estrogen; an anti-androgen; a gonadorelin agonist; a topoisomerase I inhibitor; a topoisomerase II inhibitor; a microtubule active agent; an alkylating agent, e.g., temozolomide; a retinoid, a carontenoid, or a tocopherol; a cyclooxygenase inhibitor; an MMP inhibitor; an mTOR inhibitor; an antimetabolite; a platin compound; a methionine aminopeptidase inhibitor; a bisphosphonate; an antiproliferative antibody; a heparanase inhibitor; an inhibitor of Ras oncogenic isoforms; a telomerase inhibitor; a proteasome inhibitor; a compound used in the treatment of hematologic malignancies; a Flt-3 inhibitor; an Hsp90 inhibitor; a kinesin spindle protein inhibitor; a MEK inhibitor; an antitumor antibiotic; a nitrosourea; a compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[0249] Nonlimiting exemplary aromatase inhibitors include steroids, such as atamestane, exemestane, and formestane, and non-steroids, such as aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, and letrozole.

[0250] Nonlimiting anti-estrogens include tamoxifen, fulvestrant, raloxifene, and raloxifene hydrochloride. Anti-androgens include, but are not limited to, bicalutamide and apalutamide. Gonadorelin agonists include, but are not limited to, abarelix, goserelin, and goserelin acetate.

[0251] Nonlimiting exemplary topoisomerase I inhibitors include topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin, and the macromolecular camptothecin conjugate PNU-166148. Topoisomerase II inhibitors include, but are not limited to, anthracyclines, such as doxorubicin, daunorubicin, epirubicin, idarubicin, and nemorubicin; anthraquinones, such as mitoxantrone and losoxantrone; and podophillotoxines, such as etoposide and teniposide.

[0252] Microtubule active agents include microtubule stabilizing, microtubule destabilizing compounds, and microtubulin polymerization inhibitors including, but not limited to, taxanes, such as paclitaxel and docetaxel; discodermolides; cochicine and epothilones and derivatives thereof.

[0253] Nonlimiting exemplary alkylating agents include cyclophosphamide, ifosfamide, melphalan, trabectedin, and nitrosoureas, such as carmustine and lomustine.

[0254] Nonlimiting exemplary matrix metalloproteinase inhibitors ("MMP inhibitors") include collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, batimastat, marimastat, prinomastat, metastat, BMS-279251, BAY 12-9566, TAA211, MMI270B, and AAJ996.

[0255] Nonlimiting exemplary mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[0256] Nonlimiting exemplary antimetabolites include 5-fluorouracil (5-FU), capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed.

[0257] Nonlimiting exemplary platin compounds include carboplatin, cis-platin, cisplatinum, and oxaliplatin.

[0258] Nonlimiting exemplary methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[0259] Nonlimiting exemplary bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[0260] Nonlimiting exemplary heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT2115.

[0261] Nonlimiting exemplary compounds which target, decrease, or inhibit the oncogenic activity of Ras include farnesyl transferase inhibitors, such as L-744832, DK8G557, tipifarnib, and lonafarnib.

[0262] Nonlimiting exemplary telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[0263] Nonlimiting exemplary proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomib. In some embodiments, the proteasome inhibitor is carfilzomib or ixazomib.

[0264] Nonlimiting exemplary FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R), include gilteritinib, interferon, I-β-D-arabinofuransylcytosine (ara-c),

and bisulfan; and ALK inhibitors, which are compounds that target, decrease, or inhibit anaplastic lymphoma kinase, include alectinib, brigatinib, and lorlatinib.

[0265] Nonlimiting exemplary Flt-3 inhibitors include PKC412, midostaurin, a staurosporine derivative, SU11248, MLN518, and gilteritinib.

[0266] Nonlimiting exemplary HSP90 inhibitors include compounds targeting, decreasing, or inhibiting the intrinsic ATPase activity of HSP90; or degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins, or antibodies that inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[0267] Nonlimiting exemplary protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, include a) a compound targeting, decreasing, or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as a compound that targets, decreases, or inhibits the activity of PDGFR, including olaratumab and N-phenyl-2-pyrimidine-amine derivatives, such as imatinib, SUlOl, SU6668, and GFB-111; b) a compound targeting, decreasing, or inhibiting the activity of the fibroblast growth factor-receptors (FGFR), such as erdafitinib and lenvatinib; c) a compound targeting, decreasing, or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as brigatinib; d) a compound targeting, decreasing, or inhibiting the activity of the vascular endothelial growth factor-receptors (VEGFR), such as lenvatinib; e) a compound targeting, decreasing, or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors, such as larotrectinib; f) a compound targeting, decreasing, or inhibiting the activity of the Axl receptor tyrosine kinase family; g) a compound targeting, decreasing, or inhibiting the activity of the Ret receptor tyrosine kinase, such as alectinib; h) a compound targeting, decreasing, or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; i) a compound targeting, decreasing, or inhibiting the activity of the c-Kit receptor tyrosine kinases, such as imatinib; j) a compound targeting, decreasing, or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. Bcr-Abl kinase) and mutants, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib; PD180970; AG957; NSC 680410; PD173955; or dasatinib; k) a compound targeting, decreasing, or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK,

PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK), such as a staurosporine derivative disclosed in U.S. Patent No. 5,093,330, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, bryostatin 1, perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; a isochinoline compound; a farnesyl transferase inhibitor; PD184352 or QAN697, or AT7519; abemaciclib; binimetinib; cobimetinib; encorafenib; neratinib; palbociclib; ribociclib; l) a compound targeting, decreasing or inhibiting the activity of a protein-tyrosine kinase, such as acalabrutinib, imatinib mesylate or a tyrphostin, such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); m) a compound targeting, decreasing, or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as brigatinib, CP 358774, ZD 1839, ZM 105180; trastuzumab, cetuximab, gefitinib, erlotinib, osimertinib, dacomitinib, necitumumab, neratinib, OSI-774, Cl-1033, EKB-569, GW-2016, antibodies El.l, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; n) a compound targeting, decreasing or inhibiting the activity of a phosphatidylinositol 3-kinase (PI3K), such as alpelisib, copanlisib, and duvelisib; and o) a compound targeting, decreasing, or inhibiting the activity of the c-Met receptor.

[0268] Nonlimiting exemplary compounds that target, decrease, or inhibit the activity of a protein or lipid phosphatase include inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[0269] Further anti-angiogenic compounds include compounds having another mechanism for their activity unrelated to protein or lipid kinase inhibition, e.g., thalidomide and TNP-470.

[0270] Additional, nonlimiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with a Compound of the Disclosure include: avastin, daunorubicin, adriamycin, Ara-C, VP-16, teniposide, mitoxantrone, idarubicin, carboplatinum, PKC412, 6-mercaptopurine (6-MP), fludarabine phosphate, octreotide, SOM230, FTY720, 6-thioguanine, cladribine, 6-mercaptopurine, pentostatin, hydroxyurea, 2-hydroxy-lH-isoindole-l,3-dione derivatives, l-(4-chloroanilino)-4-(4-

pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate, angiostatin, endostatin, anthranilic acid amides, ZD4190, ZD6474, SU5416, SU6668, bevacizumab, rhuMAb, rhuFab, macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, RPI 4610, porfimer sodium, anecortave, triamcinolone, hydrocortisone, 11-a-epihydrocotisol, cortex olone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone, dexamethasone, fluocinolone, a plant alkaloid, a hormonal compound and/or antagonist, a biological response modifier, such as a lymphokine or interferon, an antisense oligonucleotide or oligonucleotide derivative, shRNA, and siRNA.

[0271] A number of suitable optional therapeutic, e.g., anticancer, agents are contemplated for use in the therapeutic methods provided herein. Indeed, the methods provided herein can include, but are not limited to, administration of numerous optional therapeutic agents such as: agents that induce apoptosis; polynucleotides (*e.g.*, anti-sense, ribozymes, siRNA); polypeptides (*e.g.*, enzymes and antibodies); biological mimetics (*e.g.*, gossypol or BH3 mimetics); agents that bind (*e.g.*, oligomerize or complex) with a Bcl-2 family protein such as Bax; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal or polyclonal antibodies (*e.g.*, antibodies conjugated with anticancer drugs, toxins, defensins), toxins; radionuclides; biological response modifiers (*e.g.*, interferons (*e.g.*, IFN-α) and interleukins (*e.g.*, IL-2)); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (*e.g.*, all-trans-retinoic acid); gene therapy reagents (*e.g.*, antisense therapy reagents and nucleotides); tumor vaccines; angiogenesis inhibitors; proteosome inhibitors: NF-KB modulators; anti-CDK compounds; HDAC inhibitors; and the like. Numerous other examples of optional therapeutic agents such as chemotherapeutic compounds and anticancer therapies suitable for co-administration with the disclosed compounds are known to those skilled in the art.

[0272] In certain embodiments, anticancer agents comprise agents that induce or stimulate apoptosis. Agents that induce or stimulate apoptosis include, for example, agents that interact with or modify DNA, such as by intercalating, cross-linking, alkylating, or otherwise damaging or chemically modifying DNA. Agents that induce apoptosis include, but are not limited to, radiation (*e.g.*, X-rays, gamma rays, UV); tumor necrosis factor (TNF)-related factors (*e.g.*, TNF family receptor proteins, TNF family ligands, TRAIL, antibodies to TRAIL-R1 or TRAIL-R2); kinase inhibitors (*e.g.*,

epidermal growth factor receptor (EGFR) kinase inhibitor). Additional anticancer agents include: vascular growth factor receptor (VGFR) kinase inhibitor, fibroblast growth factor receptor (FGFR) kinase inhibitor, platelet-derived growth factor receptor (PDGFR) kinase inhibitor, and Bcr-Abl kinase inhibitors (such as GLEEVEC)); antisense molecules; antibodies (*e.g.*, HERCEPTIN, RITUXAN, ZEVALIN, and AVASTIN); anti-estrogens (*e.g.*, raloxifene and tamoxifen); anti-androgens (*e.g.*, flutamide, apalutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids); BCL-2 inhibitors (*e.g.*, venetoclax); cyclooxygenase 2 (COX-2) inhibitors (*e.g.*, celecoxib, meloxicam, NS-398, and non-steroidal anti-inflammatory drugs (NSAIDs)); anti-inflammatory drugs (*e.g.*, butazolidin, DECADRON, DELTASONE, dexamethasone, dexamethasone intensol, DEXONE, HEXADROL, hydroxychloroquine, METICORTEN, ORADEXON, ORASONE, oxyphenbutazone, PEDIAPRED, phenylbutazone, PLAQUENIL, prednisolone, prednisone, PRELONE, and TANDEARIL); and cancer chemotherapeutic drugs (*e.g.*, irinotecan (CAMPTOSAR), CPT-11, fludarabine (FLUDARA), dacarbazine (DTIC), dexamethasone, mitoxantrone, MYLOTARG, VP-16, cisplatin, carboplatin, oxaliplatin, 5-FU, doxorubicin, gemcitabine, bortezomib, gefitinib, bevacizumab, TAXOTERE or TAXOL); cellular signaling molecules; ceramides and cytokines; staurosporine, and the like.

[0273] In still other embodiments, the therapeutic methods provided herein include administering to a subject having cancer (a cancer patient) therapeutically effective amounts of a Compound of the Disclosure, an immune checkpoint inhibitor, and at least one additional optional therapeutic agent, e.g., an anti-hyperproliferative or antineoplastic agent selected from alkylating agents, antimetabolites, and natural products (*e.g.*, herbs and other plant and/or animal derived compounds).

[0274] Alkylating agents suitable for use in the present methods include, but are not limited to: 1) nitrogen mustards (*e.g.*, mechlorethamine, cyclophosphamide, ifosfamide, melphalan (L-sarcolysin); and chlorambucil); 2) ethylenimines and methylmelamines (*e.g.*, hexamethylmelamine and thiotepa); 3) alkyl sulfonates (*e.g.*, busulfan); 4) nitrosoureas (*e.g.*, carmustine (BCNU); lomustine (CCNU); semustine (methyl-CCNU); and streptozocin (streptozotocin)); and 5) triazenes (*e.g.*, dacarbazine (DTIC; dimethyltriazenoimid-azolecarboxamide).

[0275] In some embodiments, antimetabolites suitable for use in the present methods include, but are not limited to: 1) folic acid analogs (*e.g.*, methotrexate (amethopterin)); 2) pyrimidine analogs (*e.g.*, fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorode-

oxyuridine; FudR), and cytarabine (cytosine arabinoside)); and 3) purine analogs (*e.g.*, mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG), and pentostatin (2'-deoxycoformycin)).

[0276] In still further embodiments, chemotherapeutic agents suitable for use in the methods of the present disclosure include, but are not limited to: 1) vinca alkaloids (*e.g.*, vinblastine (VLB), vincristine); 2) epipodophyllotoxins (*e.g.*, etoposide and teniposide); 3) antibiotics (*e.g.*, dactinomycin (actinomycin D), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin), and mitomycin (mitomycin C)); 4) enzymes (*e.g.*, L-asparaginase); 5) biological response modifiers (*e.g.*, interferon-alfa); 6) platinum coordinating complexes (*e.g.*, cisplatin (cis-DDP) and carboplatin); 7) anthracenediones (*e.g.*, mitoxantrone); 8) substituted ureas (*e.g.*, hydroxyurea); 9) methylhydrazine derivatives (*e.g.*, procarbazine (N-methylhydrazine; MIH)); 10) adrenocortical suppressants (*e.g.*, mitotane (o,p'–DDD) and aminoglutethimide); 11) adrenocorticosteroids (*e.g.*, prednisone); 12) progestins (*e.g.*, hydroxyprogesterone caproate, medroxyprogesterone acetate, and megestrol acetate); 13) estrogens (*e.g.*, diethylstilbestrol and ethinyl estradiol); 14) antiestrogens (*e.g.*, tamoxifen); 15) androgens (*e.g.*, testosterone propionate and fluoxymesterone); 16) antiandrogens (*e.g.*, flutamide): and 17) gonadotropin-releasing hormone analogs (*e.g.*, leuprolide).

[0277] Any oncolytic agent that is routinely used in a cancer therapy context finds use in the therapeutic methods of the present disclosure. For example, the U.S. Food and Drug Administration (FDA) maintains a formulary of oncolytic agents approved for use in the United States. International counterpart agencies to the FDA maintain similar formularies. Those skilled in the art will appreciate that the "product labels" required on all U.S. approved chemotherapeutics describe approved indications, dosing information, toxicity data, and the like, for the exemplary agents.

[0278] Anticancer agents further include compounds which have been identified to have anticancer activity. Examples include, but are not limited to, 3-AP, 12-O-tetradecanoylphorbol-13-acetate, 17AAG, 852A, ABI-007, ABR-217620, ABT-751, ADI-PEG 20, AE-941, AG-013736, AGRO100, alanosine, AMG 706, antibody G250, antineoplastons, AP23573, apaziquone, APC8015, atiprimod, ATN-161, atrasenten, azacitidine, BB-10901, BCX-1777, bevacizumab, BG00001, bicalutamide, BMS 247550, bortezomib, bryostatin-1, buserelin, calaspargase pegol-mknl, calcitriol, CCI-779, CDB-2914, cefixime, cetuximab, CG0070, cilengitide, clofarabine, combretastatin A4

phosphate, CP-675,206, CP-724,714, CpG 7909, curcumin, daratumumab, decitabine, DENSPM, dinutuximab, doxercalciferol, E7070, E7389, ecteinascidin 743, efaproxiral, eflornithine, EKB-569, elotuzumab, enzastaurin, erlotinib, exisulind, fenretinide, flavopiridol, fludarabine, flutamide, fotemustine, FR901228, G17DT, galiximab, gefitinib, genistein, glasdegib, glufosfamide, GTI-2040, histrelin, HKI-272, homoharringtonine, HSPPC-96, hu14.18-interleukin-2 fusion protein, HuMax-CD4, iloprost, imiquimod, infliximab, inotuzumab ozogamicin, interleukin-12, IPI-504, irofulven, ixabepilone, lapatinib, lenalidomide, lestaurtinib, leuprolide, LMB-9 immunotoxin, lonafarnib, luniliximab, lutetium Lu 177 dotatate, mafosfamide, MB07133, MDX-010, MLN2704, mogamulizumab-kpkc, monoclonal antibody 3F8, monoclonal antibody J591, motexafin, moxetumomab pasudotox-tdfk, MS-275, MVA-MUC1-IL2, nilutamide, niraparib, nitrocamptothecin, nolatrexed dihydrochloride, nolvadex, NS-9, O6-benzylguanine, oblimersen sodium, ONYX-015, oregovomab, OSI-774, panitumumab, paraplatin, PD-0325901, pemetrexed, PHY906, pioglitazone, pirfenidone, pixantrone, polatuzumab vedotin-piiq, PS-341, PSC 833, PXD101, pyrazoloacridine, R115777, RAD001, ranpirnase, rebeccamycin analogue, rhuAngiostatin protein, rhuMab 2C4, rosiglitazone, rubitecan, rucaparib, S-1, S-8184, satraplatin, SB-, 15992, SGN-0010, SGN-40, sonidegib, sorafenib, SR31747A, ST1571, SU011248, suberoylanilide hydroxamic acid, suramin, tagraxofusp-erzs, talabostat, talampanel, talazoparib, tariquidar, temsirolimus, TGFa-PE38 immunotoxin, thalidomide, thymalfasin, tipifarnib, tirapazamine, TLK286, trabectedin, trifluridine and tipiracil hydrochloride, trimetrexate glucuronate, TroVax, UCN-1, valproic acid, vinflunine, VNP40101M, volociximab, vorinostat, VX-680, ZD1839, ZD6474, zileuton, and zosuquidar trihydrochloride.

[0279] In one embodiment, the optional therapeutic agent comprises one of the anti-cancer drugs or anti-cancer drug combinations listed in Table 6.

Table 6

Abemaciclib	Abiraterone Acetate	Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation)	ABVD
ABVE	ABVE-PC	AC	Acalabrutinib
AC-T	Actemra (Tocilizumab)	Adcetris (Brentuximab Vedotin)	ADE
Ado-Trastuzumab Emtansine	Adriamycin (Doxorubicin Hydrochloride)	Afatinib Dimaleate	Afinitor (Everolimus)

Akynzeo (Netupitant and Palonosetron Hydrochloride)	Aldara (Imiquimod)	Aldesleukin	Alecensa (Alectinib)
Alectinib	Alemtuzumab	Alimta (Pemetrexed Disodium)	Aliqopa (Copanlisib Hydrochloride)
Alkeran for Injection (Melphalan Hydrochloride)	Alkeran Tablets (Melphalan)	Aloxi (Palonosetron Hydrochloride)	Alunbrig (Brigatinib)
Ameluz (Aminolevulinic Acid)	Amifostine	Aminolevulinic Acid	Anastrozole
Apalutamide	Aprepitant	Aranesp (Darbepoetin Alfa)	Aredia (Pamidronate Disodium)
Arimidex (Anastrozole)	Aromasin (Exemestane)	Arranon (Nelarabine)	Arsenic Trioxide
Arzerra (Ofatumumab)	Asparaginase Erwinia chrysanthemi	Atezolizumab	Avastin (Bevacizumab)
Avelumab	Axicabtagene Ciloleucel	Axitinib	Azacitidine
Azedra (Iobenguane I 131)	Bavencio (Avelumab)	BEACOPP	Beleodaq (Belinostat)
Belinostat	Bendamustine Hydrochloride	Bendeka (Bendamustine Hydrochloride)	BEP
Besponsa (Inotuzumab Ozogamicin)	Bevacizumab	Bexarotene	Bicalutamide
BiCNU (Carmustine)	Binimetinib	Bleomycin	Blinatumomab
Blincyto (Blinatumomab)	Bortezomib	Bosulif (Bosutinib)	Bosutinib
Braftovi (Encorafenib)	Brentuximab Vedotin	Brigatinib	BuMel
Busulfan	Busulfex (Busulfan)	Cabazitaxel	Cabometyx (Cabozantinib-S-Malate)
Cabozantinib-S-Malate	CAF	Calquence (Acalabrutinib)	Campath (Alemtuzumab)
Camptosar (Irinotecan Hydrochloride)	Capecitabine	CAPOX	Carac (Fluorouracil--Topical)
Carboplatin	CARBOPLATIN-TAXOL	Carfilzomib	Carmustine
Carmustine Implant	Casodex (Bicalutamide)	CEM	Cemiplimab-rwlc

Ceritinib	Cerubidine (Daunorubicin Hydrochloride)	Cervarix (Recombinant HPV Bivalent Vaccine)	Cetuximab
CEV	Chlorambucil	CHLORAMBUCIL-PREDNISONE	CHOP
Cisplatin	Cladribine	Clofarabine	Clolar (Clofarabine)
CMF	Cobimetinib	Cometriq (Cabozantinib-S-Malate)	Copanlisib Hydrochloride
COPDAC	Copiktra (Duvelisib)	COPP	COPP-ABV
Cosmegen (Dactinomycin)	Cotellic (Cobimetinib)	Crizotinib	CVP
Cyclophosphamide	Cyramza (Ramucirumab)	Cytarabine	Cytarabine Liposome
Cytosar-U (Cytarabine)	Dabrafenib	Dacarbazine	Dacogen (Decitabine)
Dacomitinib	Dactinomycin	Daratumumab	Darbepoetin Alfa
Darzalex (Daratumumab)	Dasatinib	Daunorubicin Hydrochloride	Daunorubicin Hydrochloride and Cytarabine Liposome
Decitabine	Defibrotide Sodium	Defitelio (Defibrotide Sodium)	Degarelix
Denileukin Diftitox	Denosumab	DepoCyt (Cytarabine Liposome)	Dexamethasone
Dexrazoxane Hydrochloride	Dinutuximab	Docetaxel	Doxil (Doxorubicin Hydrochloride Liposome)
Doxorubicin Hydrochloride	Doxorubicin Hydrochloride Liposome	Dox-SL (Doxorubicin Hydrochloride Liposome)	Durvalumab
Duvelisib	Efudex (Fluorouracil--Topical)	Eligard (Leuprolide Acetate)	Elitek (Rasburicase)
Ellence (Epirubicin Hydrochloride)	Elotuzumab	Eloxatin (Oxaliplatin)	Eltrombopag Olamine
Emend (Aprepitant)	Empliciti (Elotuzumab)	Enasidenib Mesylate	Encorafenib
Enzalutamide	Epirubicin Hydrochloride	EPOCH	Epoetin Alfa
Epogen (Epoetin Alfa)	Erbitux (Cetuximab)	Eribulin Mesylate	Erivedge (Vismodegib)
Erleada (Apalutamide)	Erlotinib Hydrochloride	Erwinaze (Asparaginase Erwinia chrysanthemi)	Ethyol (Amifostine)

Etopophos (Etoposide Phosphate)	Etoposide	Etoposide Phosphate	Evacet (Doxorubicin Hydrochloride Liposome)
Everolimus	Evista (Raloxifene Hydrochloride)	Evomela (Melphalan Hydrochloride)	Exemestane
5-FU (Fluorouracil Injection)	5-FU (Fluorouracil--Topical)	Fareston (Toremifene)	Farydak (Panobinostat lactate)
Faslodex (Fulvestrant)	FEC	Femara (Letrozole)	Filgrastim
Firmagon (Degarelix)	Fludarabine Phosphate	Fluoroplex (Fluorouracil--Topical)	Fluorouracil Injection
Fluorouracil--Topical	Flutamide	FOLFIRI	FOLFIRI-BEVACIZUMAB
FOLFIRI-CETUXIMAB	FOLFIRINOX	FOLFOX	Folotyn (Pralatrexate)
Fostamatinib Disodium	FU-LV	Fulvestrant	Fusilev (Leucovorin Calcium)
Gardasil (Recombinant HPV Quadrivalent Vaccine)	Gardasil 9 (Recombinant HPV Nonavalent Vaccine)	Gazyva (Obinutuzumab)	Gefitinib
Gemcitabine Hydrochloride	GEMCITABINE-CISPLATIN	GEMCITABINE-OXALIPLATIN	Gemtuzumab Ozogamicin
Gemzar (Gemcitabine Hydrochloride)	Gilotrif (Afatinib Dimaleate)	Gleevec (Imatinib Mesylate)	Gliadel Wafer (Carmustine Implant)
Glucarpidase	Goserelin Acetate	Granisetron	Granisetron Hydrochloride
Granix (Filgrastim)	Halaven (Eribulin Mesylate)	Hemangeol (Propranolol Hydrochloride)	Herceptin (Trastuzumab)
HPV Bivalent Vaccine, Recombinant	HPV Nonavalent Vaccine, Recombinant	HPV Quadrivalent Vaccine, Recombinant	Hycamtin (Topotecan Hydrochloride)
Hydrea (Hydroxyurea)	Hydroxyurea	Hyper-CVAD	Ibrance (Palbociclib)
Ibritumomab Tiuxetan	Ibrutinib	ICE	Iclusig (Ponatinib Hydrochloride)
Idarubicin Hydrochloride	Idelalisib	Idhifa (Enasidenib Mesylate)	Ifex (Ifosfamide)
Ifosfamide	IL-2 (Aldesleukin)	Imatinib Mesylate	Imbruvica (Ibrutinib)
Imfinzi (Durvalumab)	Imiquimod	Imlygic (Talimogene Laherparepvec)	Inlyta (Axitinib)
Inotuzumab Ozogamicin	Interferon Alfa-2b, Recombinant	Interleukin-2 (Aldesleukin)	Intron A (Recombinant Interferon Alfa-2b)

Iobenguane I 131	Ipilimumab	Iressa (Gefitinib)	Irinotecan Hydrochloride
Irinotecan Hydrochloride Liposome	Istodax (Romidepsin)	Ivosidenib	Ixabepilone
Ixazomib Citrate	Ixempra (Ixabepilone)	Jakafi (Ruxolitinib Phosphate)	JEB
Jevtana (Cabazitaxel)	Kadcyla (Ado-Trastuzumab Emtansine)	Kepivance (Palifermin)	Keytruda (Pembrolizumab)
Kisqali (Ribociclib)	Kymriah (Tisagenlecleucel)	Kyprolis (Carfilzomib)	Lanreotide Acetate
Lapatinib Ditosylate	Larotrectinib Sulfate	Lartruvo (Olaratumab)	Lenalidomide
Lenvatinib Mesylate	Lenvima (Lenvatinib Mesylate)	Letrozole	Leucovorin Calcium
Leukeran (Chlorambucil)	Leuprolide Acetate	Levulan Kerastik (Aminolevulinic Acid)	Libtayo (Cemiplimab-rwlc)
LipoDox (Doxorubicin Hydrochloride Liposome)	Lomustine	Lonsurf (Trifluridine and Tipiracil Hydrochloride)	Lorbrena (Lorlatinib)
Lorlatinib	Lumoxiti (Moxetumomab Pasudotox-tdfk)	Lupron (Leuprolide Acetate)	Lupron Depot (Leuprolide Acetate)
Lutathera (Lutetium Lu 177-Dotatate)	Lutetium (Lu 177-Dotatate)	Lynparza (Olaparib)	Marqibo (Vincristine Sulfate Liposome)
Matulane (Procarbazine Hydrochloride)	Mechlorethamine Hydrochloride	Megestrol Acetate	Mekinist (Trametinib)
Mektovi (Binimetinib)	Melphalan	Melphalan Hydrochloride	Mercaptopurine
Mesna	Mesnex (Mesna)	Methotrexate	Methylnaltrexone Bromide
Midostaurin	Mitomycin C	Mitoxantrone Hydrochloride	Mogamulizumab-kpkc
Moxetumomab Pasudotox-tdfk	Mozobil (Plerixafor)	Mustargen (Mechlorethamine Hydrochloride)	MVAC
Myleran (Busulfan)	Mylotarg (Gemtuzumab Ozogamicin)	Nanoparticle Paclitaxel (Paclitaxel Albumin-stabilized Nanoparticle Formulation)	Navelbine (Vinorelbine Tartrate)
Necitumumab	Nelarabine	Neratinib Maleate	Nerlynx (Neratinib Maleate)

Netupitant and Palonosetron Hydrochloride	Neulasta (Pegfilgrastim)	Neupogen (Filgrastim)	Nexavar (Sorafenib Tosylate)
Nilandron (Nilutamide)	Nilotinib	Nilutamide	Ninlaro (Ixazomib Citrate)
Niraparib Tosylate Monohydrate	Nivolumab	Nplate (Romiplostim)	Obinutuzumab
Odomzo (Sonidegib)	OEPA	Ofatumumab	OFF
Olaparib	Olaratumab	Omacetaxine Mepesuccinate	Oncaspar (Pegaspargase)
Ondansetron Hydrochloride	Onivyde (Irinotecan Hydrochloride Liposome)	Ontak (Denileukin Diftitox)	Opdivo (Nivolumab)
OPPA	Osimertinib	Oxaliplatin	Paclitaxel
Paclitaxel Albumin-stabilized Nanoparticle Formulation	PAD	Palbociclib	Palifermin
Palonosetron Hydrochloride	Palonosetron Hydrochloride and Netupitant	Pamidronate Disodium	Panitumumab
Panobinostat Lactate	Pazopanib Hydrochloride	PCV	PEB
Pegaspargase	Pegfilgrastim	Peginterferon Alfa-2b	PEG-Intron (Peginterferon Alfa-2b)
Pembrolizumab	Pemetrexed Disodium	Perjeta (Pertuzumab)	Pertuzumab
Plerixafor	Pomalidomide	Pomalyst (Pomalidomide)	Ponatinib Hydrochloride
Portrazza (Necitumumab)	Poteligeo (Mogamulizumab-kpkc)	Pralatrexate	Prednisone
Procarbazine Hydrochloride	Procrit (Epoetin Alfa)	Proleukin (Aldesleukin)	Prolia (Denosumab)
Promacta (Eltrombopag Olamine)	Propranolol Hydrochloride	Provenge (Sipuleucel-T)	Purinethol (Mercaptopurine)
Purixan (Mercaptopurine)	Radium 223 Dichloride	Raloxifene Hydrochloride	Ramucirumab
Rasburicase	R-CHOP	R-CVP	Recombinant Human Papillomavirus (HPV) Bivalent Vaccine

Recombinant Human Papillomavirus (HPV) Nonavalent Vaccine	Recombinant Human Papillomavirus (HPV) Quadrivalent Vaccine	Recombinant Interferon Alfa-2b	Regorafenib
Relistor (Methylnaltrexone Bromide)	R-EPOCH	Retacrit (Epoetin Alfa)	Revlimid (Lenalidomide)
Rheumatrex (Methotrexate)	Ribociclib	R-ICE	Rituxan (Rituximab)
Rituxan Hycela (Rituximab and Hyaluronidase Human)	Rituximab	Rituximab and Hyaluronidase Human	Rolapitant Hydrochloride
Romidepsin	Romiplostim	Rubidomycin (Daunorubicin Hydrochloride)	Rubraca (Rucaparib Camsylate)
Rucaparib Camsylate	Ruxolitinib Phosphate	Rydapt (Midostaurin)	Sancuso (Granisetron)
Sclerosol Intrapleural Aerosol (Talc)	Siltuximab	Sipuleucel-T	Somatuline Depot (Lanreotide Acetate)
Sonidegib	Sorafenib Tosylate	Sprycel (Dasatinib)	STANFORD V
Sterile Talc Powder (Talc)	Steritalc (Talc)	Stivarga (Regorafenib)	Sunitinib Malate
Sustol (Granisetron)	Sutent (Sunitinib Malate)	Sylatron (Peginterferon Alfa-2b)	Sylvant (Siltuximab)
Synribo (Omacetaxine Mepesuccinate)	Tabloid (Thioguanine)	TAC	Tafinlar (Dabrafenib)
Tagrisso (Osimertinib)	Talc	Talimogene Laherparepvec	Tamoxifen Citrate
Tarabine PFS (Cytarabine)	Tarceva (Erlotinib Hydrochloride)	Targretin (Bexarotene)	Tasigna (Nilotinib)
Tavalisse (Fostamatinib Disodium)	Taxol (Paclitaxel)	Taxotere (Docetaxel)	Tecentriq (Atezolizumab)
Temodar (Temozolomide)	Temozolomide	Temsirolimus	Thalidomide
Thalomid (Thalidomide)	Thioguanine	Thiotepa	Tibsovo (Ivosidenib)
Tisagenlecleucel	Tocilizumab	Tolak (Fluorouracil--Topical)	Topotecan Hydrochloride
Toremifene	Torisel (Temsirolimus)	Totect (Dexrazoxane Hydrochloride)	TPF
Trabectedin	Trametinib	Trastuzumab	Treanda (Bendamustine Hydrochloride)

Trexall (Methotrexate)	Trifluridine and Tipiracil Hydrochloride	Trisenox (Arsenic Trioxide)	Tykerb (Lapatinib Ditosylate)
Unituxin (Dinutuximab)	Uridine Triacetate	VAC	Valrubicin
Valstar (Valrubicin)	Vandetanib	VAMP	Varubi (Rolapitant Hydrochloride)
Vectibix (Panitumumab)	VeIP	Velcade (Bortezomib)	Vemurafenib
Venclexta (Venetoclax)	Venetoclax	Verzenio (Abemaciclib)	Vidaza (Azacitidine)
Vinblastine Sulfate	Vincristine Sulfate	Vincristine Sulfate Liposome	Vinorelbine Tartrate
VIP	Vismodegib	Vistogard (Uridine Triacetate)	Vitrakvi (Larotrectinib Sulfate)
Vizimpro (Dacomitinib)	Voraxaze (Glucarpidase)	Vorinostat	Votrient (Pazopanib Hydrochloride)
Vyxeos (Daunorubicin Hydrochloride and Cytarabine Liposome)	Xalkori (Crizotinib)	Xeloda (Capecitabine)	XELIRI
XELOX	Xgeva (Denosumab)	Xofigo (Radium 223 Dichloride)	Xtandi (Enzalutamide)
Yervoy (Ipilimumab)	Yescarta (Axicabtagene Ciloleucel)	Yondelis (Trabectedin)	Zaltrap (Ziv-Aflibercept)
Zarxio (Filgrastim)	Zejula (Niraparib Tosylate Monohydrate)	Zelboraf (Vemurafenib)	Zevalin (Ibritumomab Tiuxetan)
Zinecard (Dexrazoxane Hydrochloride)	Ziv-Aflibercept	Zofran (Ondansetron Hydrochloride)	Zoladex (Goserelin Acetate)
Zoledronic Acid	Zolinza (Vorinostat)	Zometa (Zoledronic Acid)	Zydelig (Idelalisib)
Zykadia (Ceritinib)	Zytiga (Abiraterone Acetate)		

[0280] The disclosure provides the following particular embodiments in connection with treating a disease in a subject.

[0281] Embodiment I. A method of treating a subject, the method comprising administering to the subject a therapeutically effective amount of a Compound of the

Disclosure or PROTAC Molecule, wherein the subject has cancer or other proliferative disorder, or an inflammatory disease.

[0282] Embodiment II. The method Embodiment I, wherein the subject has cancer.

[0283] Embodiment III. The method of Embodiment II, wherein the cancer is any one or more of the cancers of Table 4.

[0284] Embodiment IV. The method of Embodiment II, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

[0285] Embodiment V. The method of Embodiment II, wherein the cancer is any one or more of the cancers of Table 5, e.g, multiple myeloma.

[0286] Embodiment VI. The method of any one of Embodiments I-V further comprising administering a therapeutically effective amount of an optional therapeutic agent useful in the treatment of the disease or condition, e.g., an immune checkpoint inhibitor or other anticancer agent.

[0287] Embodiment VII. The method of any one of Embodiments I-VI, wherein the Compound of the Disclosure is a compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0288] Embodiment VIII. The method of any one of Embodiments I-VI, wherein the Compound of the Disclosure is a compound of any one of Formulae **II-IV**, or a pharmaceutically acceptable salt or solvate thereof.

[0289] Embodiment IX. A pharmaceutical composition comprising a Compound of the Disclosure or PROTAC Molecule, and a pharmaceutically acceptable excipient for use in treating cancer or other proliferative disorder, or an inflammatory disease.

[0290] Embodiment X. The pharmaceutical composition of Embodiment IX for use in treating cancer.

[0291] Embodiment XI. The pharmaceutical composition of Embodiment X, wherein the cancer is any one or more of the cancers of Table 4.

[0292] Embodiment XII. The pharmaceutical composition of Embodiment X, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia

mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

[0293] Embodiment XIII. The pharmaceutical composition of Embodiment X, wherein the cancer is any one or more of the cancers of Table 5.

[0294] Embodiment XIV. The pharmaceutical composition of any one of Embodiments IX-XIII, wherein the Compound of the Disclosure is a compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0295] Embodiment XV. The pharmaceutical composition of any one of Embodiments IX-XIII, wherein the Compound of the Disclosure is a compound of any one of Formulae **II-IV**, or a pharmaceutically acceptable salt or solvate thereof.

[0296] Embodiment XVI. A Compound of the Disclosure or PROTAC Molecule for use in treatment of cancer or other proliferative disorder, or an inflammatory disease.

[0297] Embodiment XVII. The compound of Embodiment XVI for use in treating cancer.

[0298] Embodiment XVIII. The compound of Embodiment XVII, wherein the cancer is any one or more of the cancers of Table 4.

[0299] Embodiment XIX. The compound of Embodiment XVII, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

[0300] Embodiment XX. The compound of Embodiment XVII, wherein the cancer is any one or more of the cancers of Table 5.

[0301] Embodiment XXI. The compound of any one of Embodiments XVI-XX, wherein the Compound of the Disclosure is a compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0302] Embodiment XXII. The compound of any one of Embodiments XVI-XX, wherein the Compound of the Disclosure is a compound of any one of Formulae **II-IV**, or a pharmaceutically acceptable salt or solvate thereof.

[0303] Embodiment XXIII. Use of a Compound of the Disclosure or PROTAC Molecule for the manufacture of a medicament for treatment of cancer or other proliferative disorder, or an inflammatory disease.

[0304] Embodiment XXIV. The use of Embodiment XXIII for the treatment of cancer.

[0305] Embodiment XXV. The use of Embodiment XXIV, wherein the cancer is any one or more of the cancers of Table 4.

[0306] Embodiment XXVI. The use of Embodiment XXIII, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

[0307] Embodiment XXVII. The use of Embodiment XXIV, wherein the cancer is any one or more of the cancers of Table 5.

[0308] Embodiment XXVIII. The use of any one of Embodiments XXIII-XXVII, wherein the Compound of the Disclosure is a compound of any one of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0309] Embodiment XXIX. The use of any one of Embodiments XXIII-XXVII, wherein the Compound of the Disclosure is a compound of any one of Formulae **II-IV**, or a pharmaceutically acceptable salt or solvate thereof.

[0310] Embodiment XXX. A method of inhibiting CRBN ubiquitination within a cell of a subject in need thereof, the method comprising administering to the subject a compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0311] Embodiment XXXI. A method of inhibiting CRBN ubiquitination within a cell of a subject in need thereof, the method comprising administering to the subject a compound of any one of Formulae **II-IV**, or a pharmaceutically acceptable salt or solvate thereof.

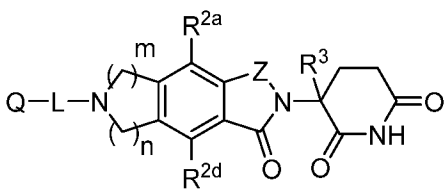
V. Kits of the Disclosure

[0312] In another embodiment, the present disclosure provides kits which comprise a Compound of the Disclosure or PROTAC Molecule (or a composition comprising a Compound of the Disclosure or PROTAC Molecule) packaged in a manner that facilitates their use to practice methods of the present disclosure. In one embodiment, the kit includes a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the disclosure, e.g., the method of any one of Embodiments I-VI. In one embodiment, the compound or composition is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

VI. PROTAC Molecules

[0313] Proteolysis-targeting chimera (PROTAC) is a useful technology for targeted protein degradation. A bifunctional PROTAC molecule consists of a ligand (usually a small-molecule inhibitor) of the protein of interest and a covalently linked ligand of an E3 ubiquitin ligase. Upon binding to the protein of interest, the PROTAC can recruit E3 ubiquitin ligase for ubiquitination of the protein of interest, which is subjected to proteasome-mediated degradation. *See, e.g.*, Bondeson and Crews, *Annu Rev Pharmacol Toxicol. 57*:107-123 (2017); Sun et al., *Sig Transduct Target Ther 4*:64 (2019) https://doi.org/10.1038/s41392-019-0101-6; Li and Song, *J Hematol Oncol 13*: 50 (2020) https://doi.org/10.1186/s13045-020-00885-3; Wang et al., *Acta Pharmaceutica Sinica B 10*:207-238 (2020). Compounds of the Disclosure can be tethered to a moiety of interest, e.g., ligand that binds to a protein, e.g., small molecule inhibitor of a protein, to give a PROTAC molecule.

[0314] In one embodiment, PROTAC Molecules are compounds of Formula **XXIII**:



XXIII,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0315] R^{2a}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**;

[0316] Q is a moiety of interest; and

[0317] L is $-J^1-J^2-J^3-J^4-J^5-$, wherein J^1 is attached to Q;

[0318] J^1 is selected from the group consisting of alkylenyl, cycloalkylenyl, and heterocyclenyl; or J^1 is absent;

[0319] J^2 is selected from the group consisting of -C(=O)-, -$(CH_2)_q$-, -CH=CH-, and -C≡C-;

[0320] q is 0, 1, 2, or 3;

[0321] J^3 is selected from the group consisting of alkylenyl, heteroalkylenyl, cycloalkylenyl, heterocyclenyl, phenylenyl, and heteroarylenyl; or J^3 is absent;

[0322] J^4 is selected from the group consisting of alkylenyl, cycloalkylenyl, and heterocyclenyl; or J^4 is absent;

[0323] J^5 is selected from the group consisting of -$(CH_2)_r$- and -C(=O)-; and

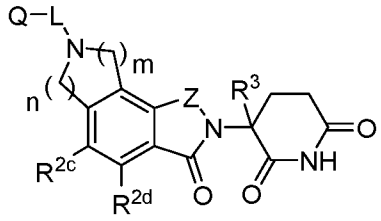
[0324] r is 0, 1, 2, or 3.

[0325] In another embodiment, PROTAC Molecules are compounds of Formula **XXIII**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0326] In another embodiment, PROTAC Molecules are compounds of Formula **XXIII**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0327] In another embodiment, PROTAC Molecules are compounds of Formula **XXIII**, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2d} are hydrogen.

[0328] In another embodiment, PROTAC Molecules are compounds of Formula **XXIV**:



XXIV,

or a pharmaceutically acceptable salt or solvate thereof, wherein L and Q are as defined in connection with Formula **XXIII**; and R^{2c}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**.

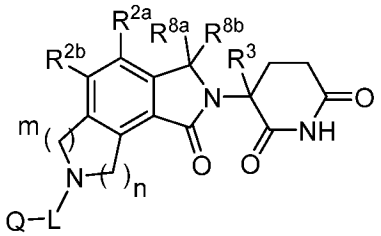
[0329] In another embodiment, PROTAC Molecules are compounds of Formula **XXIV**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0330] In another embodiment, PROTAC Molecules are compounds of Formula **XXIV**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0331] In another embodiment, PROTAC Molecules are compounds of Formula **XXIV**, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen,

fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2c} and R^{2d} are hydrogen.

[0332] In another embodiment, PROTAC Molecules are compounds of Formula **XXV**:



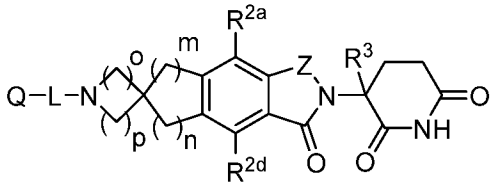
XXV,

or a pharmaceutically acceptable salt or solvate thereof, wherein L and Q are as defined in connection with Formula **XXIII**; and R^{2a}, R^{2b}, R^3, R^{8a}, R^{8b}, m, n, and Z are as defined in connection with Formula **I**.

[0333] In another embodiment, PROTAC Molecules are compounds of Formula **XXV**, wherein R^{8a} and R^{8b} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0334] In another embodiment, PROTAC Molecules are compounds of Formula **XXV**, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2b} are hydrogen.

[0335] In another embodiment, PROTAC Molecules are compounds of Formula **XXVI**:



XXVI,

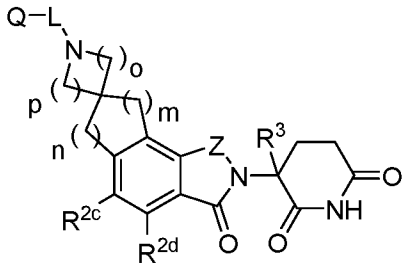
or a pharmaceutically acceptable salt or solvate thereof, wherein L and Q are as defined in connection with Formula **XXIII**; and R^{2a}, R^{2d}, R^3, m, n, o, p, and Z are as defined in connection with Formula **I**.

[0336] In another embodiment, PROTAC Molecules are compounds of Formula **XXVI**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0337] In another embodiment, PROTAC Molecules are compounds of Formula **XXVI**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0338] In another embodiment, PROTAC Molecules are compounds of Formula **XXVI**, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2d} are hydrogen.

[0339] In another embodiment, PROTAC Molecules are compounds of Formula **XXVII**:



XXVII,

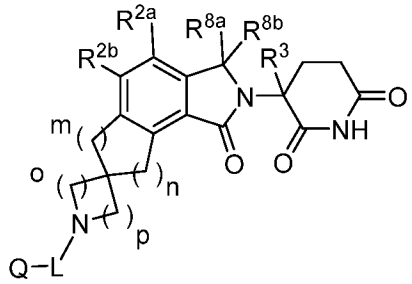
or a pharmaceutically acceptable salt or solvate thereof, wherein L and Q are as defined in connection with Formula **XXIII**; and R^{2c}, R^{2d}, R^3, m, n, o, p, and Z are as defined in connection with Formula **I**.

[0340] In another embodiment, PROTAC Molecules are compounds of Formula **XXVII**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0341] In another embodiment, PROTAC Molecules are compounds of Formula **XXVII**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0342] In another embodiment, PROTAC Molecules are compounds of Formula **XXVII**, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2c} and R^{2d} are hydrogen.

[0343] In another embodiment, PROTAC Molecules are compounds of Formula **XXVIII**:



XXVIII,

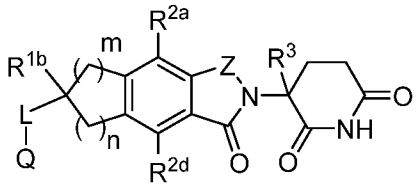
or a pharmaceutically acceptable salt or solvate thereof, wherein L and Q are as defined in connection with Formula **XXIII**; and R^{2a}, R^{2b}, R^3, R^{8a}, R^{8b}, m, n, o, p, and Z are as defined in connection with Formula **I**.

[0344] In another embodiment, PROTAC Molecules are compounds of Formula **XXVIII**, wherein R^{8a} and R^{8b} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0345] In another embodiment, PROTAC Molecules are compounds of Formula **XXVIII**, wherein R^{2a} and R^{2b} are independently selected from the group

consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2b} are hydrogen.

[0346] In another embodiment, PROTAC Molecules are compounds of Formula **XXIX**:



XXIX,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0347] Q is as defined in connection with Formula **XXIII**;

[0348] R^{1b}, R^{2a}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**;

[0349] L is $-J^1-J^2-J^3-J^4-J^5-$, wherein J^1 is attached to Q;

[0350] J^1, J^2, J^3, J^4 are as defined in connection with Formula **XXIII**;

[0351] J^5 is selected from the group consisting of -C≡C-, $-(CH_2)_r-$, -O-, $-N(R^{14})-$, and -C(=O)-;

[0352] r is 0, 1, 2, or 3; and

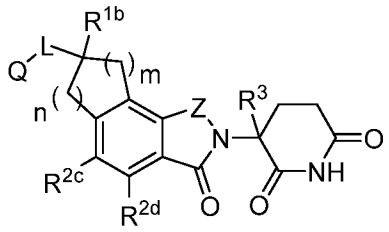
[0353] R^{14} is selected from the group consisting of hydrogen and C_1-C_3 alkyl.

[0354] In another embodiment, PROTAC Molecules are compounds of Formula **XXIX**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0355] In another embodiment, PROTAC Molecules are compounds of Formula **XXIX**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0356] In another embodiment, PROTAC Molecules are compounds of Formula **XXIX**, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2d} are hydrogen.

[0357] In another embodiment, PROTAC Molecules are compounds of Formula **XXX**:



XXX,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0358] Q is as defined in connection with Formula **XXIII**;

[0359] R^{1b}, R^{2c}, R^{2d}, R^3, m, n, and Z are as defined in connection with Formula **I**;

[0360] L is $-J^1-J^2-J^3-J^4-J^5-$, wherein J^1 is attached to Q;

[0361] J^1, J^2, J^3, J^4 are as defined in connection with Formula **XXIII**; and

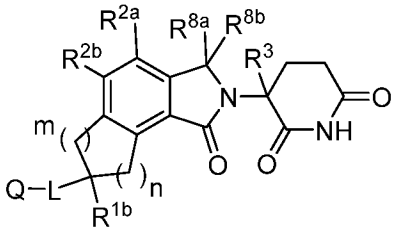
[0362] J^5 is as defined in connection with Formula **XXIX**.

[0363] In another embodiment, PROTAC Molecules are compounds of Formula **XXX**, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

[0364] In another embodiment, PROTAC Molecules are compounds of Formula **XXX**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0365] In another embodiment, PROTAC Molecules are compounds of Formula **XXX**, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2c} and R^{2d} are hydrogen.

[0366] In another embodiment, PROTAC Molecules are compounds of Formula **XXXI**:



XXXI,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0367] Q is as defined in connection with Formula **XXIII**;

[0368] R^{1b}, R^{2a}, R^{2b}, R^3, R^{8a}, R^{8b}, m, n, and Z are as defined in connection with Formula **I**;

[0369] L is -J^1-J^2-J^3-J^4-J^5-, wherein J^1 is attached to Q;

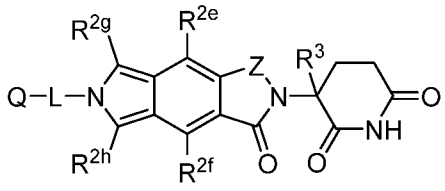
[0370] J^1, J^2, J^3, J^4 are as defined in connection with Formula **XXIII**; and

[0371] J^5 is as defined in connection with Formula **XXIX**.

[0372] In another embodiment, PROTAC Molecules are compounds of Formula **XXXI**, wherein R^{8a} and R^{8b} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0373] In another embodiment, PROTAC Molecules are compounds of Formula **XXXI**, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2a} and R^{2b} are hydrogen.

[0374] In another embodiment, PROTAC Molecules are compounds of Formula **XXXII**:



XXXII,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0375] L and Q are as defined in connection with Formula **XXIII**;

[0376] R^{2e}, R^{2f}, R^{2g}, and R^{2h} are as defined in connection with Formula **XVIII**; and

[0377] R^3 and Z as defined in connection with Formula **I**.

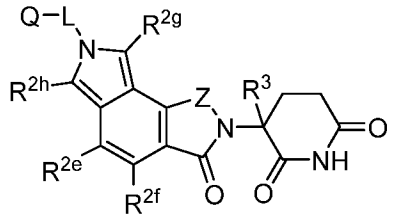
[0378] In another embodiment, PROTAC Molecules are compounds of Formula **XXXII**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0379] In another embodiment, PROTAC Molecules are compounds of Formula **XXXII**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0380] In another embodiment, PROTAC Molecules are compounds of Formula **XXXII**, wherein R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen and halo, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2e} and R^{2f} are hydrogen.

[0381] In another embodiment, PROTAC Molecules are compounds of Formula **XXXII**, wherein R^{2g} and R^{2h} are independently selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2g} and R^{2h} are hydrogen.

[0382] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIII**:



XXXIII,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0383] L and Q are as defined in connection with Formula **XXIII**;

[0384] R^{2e}, R^{2f}, R^{2g}, and R^{2h} are as defined in connection with Formula **XVIII**; and

[0385] R^3 and Z as defined in connection with Formula **I**.

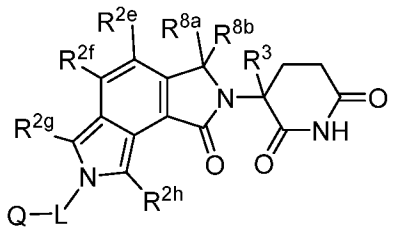
[0386] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIII**, wherein Z is $-CH_2-$, or a pharmaceutically acceptable salt or solvate thereof.

[0387] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIII**, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

[0388] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIII**, wherein R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen and halo, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2e} and R^{2f} are hydrogen.

[0389] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIII**, wherein R^{2g} and R^{2h} are independently selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2g} and R^{2h} are hydrogen

[0390] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIV**:



XXXIV,

[0391] or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0392] L and Q are as defined in connection with Formula **XXIII**;

[0393] R^{2e}, R^{2f}, R^{2g}, and R^{2h} are as defined in connection with Formula **XVIII**; and

[0394] R^3, R^{8a}, R^{8b}, and Z as defined in connection with Formula **I**.

[0395] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIV**, wherein R^{8a} and R^{8b} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0396] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIV**, wherein R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen and halo, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2e} and R^{2f} are hydrogen.

[0397] In another embodiment, PROTAC Molecules are compounds of Formula **XXXIV**, wherein R^{2g} and R^{2h} are independently selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, R^{2g} and R^{2h} are hydrogen.

[0398] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIII-XXVIII** or **XXXII-XXXIV**, or a pharmaceutically acceptable salt or solvate thereof, wherein L is any one or more of the -J^1-, -J^1-J^2-, -J^1-J^2-J^3-, or J^1-J^2-J^3-J^4- groups listed in Table 9.

[0399] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIX-XXXI**, or a pharmaceutically acceptable salt or solvate thereof, wherein L is any one or more of the --J^1-, -J^1-J^2-, -J^1-J^2-J^3-, J^1-J^2-J^3-J^4- or -, J^1-J^2-J^3-J^4-J^5- groups listed in Table 9.

Table 9

No.	J^1	J^2	J^3	J^4	J^5
1	alkylenyl	-	-	-	-
2	cycloalkylenyl	-	-	-	-
3	heterocyclenyl	-	-	-	-
4	-	-C(=O)-	-	-	-
5	alkylenyl	-C(=O)-	-	-	-
6	cycloalkylenyl	-C(=O)-	-	-	-
7	heterocyclenyl	-C(=O)-	-	-	-
8	-	-C(=O)NH-	-	-	-
9	alkylenyl	-C(=O)NH-	-	-	-
10	cycloalkylenyl	-C(=O)NH-	-	-	-
11	heterocyclenyl	-C(=O)NH-	-	-	-
12	-	-C≡C-	-	-	-
13	alkylenyl	-C≡C-	-	-	-
14	cycloalkylenyl	-C≡C-	-	-	-
15	heterocyclenyl	-C≡C-	-	-	-
16	alkylenyl	-	heterocyclenyl	-	-
17	cycloalkylenyl	-	heterocyclenyl	-	-
18	heterocyclenyl	-	heterocyclenyl	-	-
19	-	-C(=O)-	heterocyclenyl	-	-
20	alkylenyl	-C(=O)-	heterocyclenyl	-	-
21	cycloalkylenyl	-C(=O)-	heterocyclenyl	-	-
22	heterocyclenyl	-C(=O)-	heterocyclenyl	-	-

23	-	-C(=O)NH-	heterocyclenyl	-	-
24	alkylenyl	-C(=O)NH-	heterocyclenyl	-	-
25	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	-	-
26	heterocyclenyl	-C(=O)NH-	heterocyclenyl	-	-
27	-	-C≡C-	heterocyclenyl	-	-
28	alkylenyl	-C≡C-	heterocyclenyl	-	-
29	cycloalkylenyl	-C≡C-	heterocyclenyl	-	-
30	heterocyclenyl	-C≡C-	heterocyclenyl	-	-
31	cycloalkylenyl	-	alkylenyl	heterocyclenyl	-
32	heterocyclenyl	-	alkylenyl	heterocyclenyl	-
33	-	-C(=O)-	alkylenyl	heterocyclenyl	-
34	alkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-
35	cycloalkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-
36	heterocyclenyl	-C(=O)-	alkylenyl	heterocyclenyl	-
37	-	-C(=O)NH-	alkylenyl	heterocyclenyl	-
38	alkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-
39	cycloalkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-
40	heterocyclenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-
41	-	-C≡C-	alkylenyl	heterocyclenyl	-
42	alkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-
43	cycloalkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-
44	heterocyclenyl	-C≡C-	alkylenyl	heterocyclenyl	-
45	alkylenyl	-	cycloalkylenyl	heterocyclenyl	-
46	cycloalkylenyl	-	cycloalkylenyl	heterocyclenyl	-
47	heterocyclenyl	-	cycloalkylenyl	heterocyclenyl	-
48	-	-C(=O)-	cycloalkylenyl	heterocyclenyl	-
49	alkylenyl	-C(=O)-	cycloalkylenyl	heterocyclenyl	-
50	cycloalkylenyl	-C(=O)-	cycloalkylenyl	heterocyclenyl	-
51	heterocyclenyl	-C(=O)-	cycloalkylenyl	heterocyclenyl	-
52	-	-C(=O)NH-	cycloalkylenyl	heterocyclenyl	-
53	alkylenyl	-C(=O)NH-	cycloalkylenyl	heterocyclenyl	-
54	cycloalkylenyl	-C(=O)NH-	cycloalkylenyl	heterocyclenyl	-
55	heterocyclenyl	-C(=O)NH-	cycloalkylenyl	heterocyclenyl	-

56	-	-C≡C-	cycloalkylenyl	heterocyclenyl	-
57	alkylenyl	-C≡C-	cycloalkylenyl	heterocyclenyl	-
58	cycloalkylenyl	-C≡C-	cycloalkylenyl	heterocyclenyl	-
59	heterocyclenyl	-C≡C-	cycloalkylenyl	heterocyclenyl	-
60	alkylenyl	-	phenylenyl	heterocyclenyl	-
61	cycloalkylenyl	-	phenylenyl	heterocyclenyl	-
62	heterocyclenyl	-	phenylenyl	heterocyclenyl	-
63	-	-C(=O)-	phenylenyl	heterocyclenyl	-
64	alkylenyl	-C(=O)-	phenylenyl	heterocyclenyl	-
65	cycloalkylenyl	-C(=O)-	phenylenyl	heterocyclenyl	-
66	heterocyclenyl	-C(=O)-	phenylenyl	heterocyclenyl	-
67	-	-C(=O)NH-	phenylenyl	heterocyclenyl	-
68	alkylenyl	-C(=O)NH-	phenylenyl	heterocyclenyl	-
69	cycloalkylenyl	-C(=O)NH-	phenylenyl	heterocyclenyl	-
70	heterocyclenyl	-C(=O)NH-	phenylenyl	heterocyclenyl	-
71	-	-C≡C-	phenylenyl	heterocyclenyl	-
72	alkylenyl	-C≡C-	phenylenyl	heterocyclenyl	-
73	cycloalkylenyl	-C≡C-	phenylenyl	heterocyclenyl	-
74	heterocyclenyl	-C≡C-	phenylenyl	heterocyclenyl	-
75	cycloalkylenyl	-	alkylenyl	-	-C≡C-
76	heterocyclenyl	-	alkylenyl	-	-C≡C-
77	-	-C(=O)-	alkylenyl	-	-C≡C-
78	alkylenyl	-C(=O)-	alkylenyl	-	-C≡C-
79	cycloalkylenyl	-C(=O)-	alkylenyl	-	-C≡C-
80	heterocyclenyl	-C(=O)-	alkylenyl	-	-C≡C-
81	-	-C(=O)NH-	alkylenyl	-	-C≡C-
82	alkylenyl	-C(=O)NH-	alkylenyl	-	-C≡C-
83	cycloalkylenyl	-C(=O)NH-	alkylenyl	-	-C≡C-
84	heterocyclenyl	-C(=O)NH-	alkylenyl	-	-C≡C-
85	-	-C≡C-	alkylenyl	-	-C≡C-
86	alkylenyl	-C≡C-	alkylenyl	-	-C≡C-
87	cycloalkylenyl	-C≡C-	alkylenyl	-	-C≡C-
88	heterocyclenyl	-C≡C-	alkylenyl	-	-C≡C-

89	-	-	heteroalkylenyl	-	-C≡C-
90	alkylenyl	-	heteroalkylenyl	-	-C≡C-
91	cycloalkylenyl	-	heteroalkylenyl	-	-C≡C-
92	heterocyclenyl	-	heteroalkylenyl	-	-C≡C-
93	-	-C(=O)-	heteroalkylenyl	-	-C≡C-
94	alkylenyl	-C(=O)-	heteroalkylenyl	-	-C≡C-
95	cycloalkylenyl	-C(=O)-	heteroalkylenyl	-	-C≡C-
96	heterocyclenyl	-C(=O)-	heteroalkylenyl	-	-C≡C-
97	-	-C(=O)NH-	heteroalkylenyl	-	-C≡C-
98	alkylenyl	-C(=O)NH-	heteroalkylenyl	-	-C≡C-
99	cycloalkylenyl	-C(=O)NH-	heteroalkylenyl	-	-C≡C-
100	heterocyclenyl	-C(=O)NH-	heteroalkylenyl	-	-C≡C-
101	-	-C≡C-	heteroalkylenyl	-	-C≡C-
102	alkylenyl	-C≡C-	heteroalkylenyl	-	-C≡C-
103	cycloalkylenyl	-C≡C-	heteroalkylenyl	-	-C≡C-
104	heterocyclenyl	-C≡C-	heteroalkylenyl	-	-C≡C-
105	alkylenyl	-	heterocyclenyl	-	-C≡C-
106	cycloalkylenyl	-	heterocyclenyl	-	-C≡C-
107	heterocyclenyl	-	heterocyclenyl	-	-C≡C-
108	-	-C(=O)-	heterocyclenyl	-	-C≡C-
109	alkylenyl	-C(=O)-	heterocyclenyl	-	-C≡C-
110	cycloalkylenyl	-C(=O)-	heterocyclenyl	-	-C≡C-
111	heterocyclenyl	-C(=O)-	heterocyclenyl	-	-C≡C-
112	-	-C(=O)NH-	heterocyclenyl	-	-C≡C-
113	alkylenyl	-C(=O)NH-	heterocyclenyl	-	-C≡C-
114	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	-	-C≡C-
115	heterocyclenyl	-C(=O)NH-	heterocyclenyl	-	-C≡C-
116	-	-C≡C-	heterocyclenyl	-	-C≡C-
117	alkylenyl	-C≡C-	heterocyclenyl	-	-C≡C-
118	cycloalkylenyl	-C≡C-	heterocyclenyl	-	-C≡C-
119	heterocyclenyl	-C≡C-	heterocyclenyl	-	-C≡C-
120	alkylenyl	-	alkylenyl	heterocyclenyl	-C≡C-
121	cycloalkylenyl	-	alkylenyl	heterocyclenyl	-C≡C-

122	heterocyclenyl	-	alkylenyl	heterocyclenyl	-C≡C-
123	-	-C(=O)-	alkylenyl	heterocyclenyl	-C≡C-
124	alkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-C≡C-
125	cycloalkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-C≡C-
126	heterocyclenyl	-C(=O)-	alkylenyl	heterocyclenyl	-C≡C-
127	-	-C(=O)NH-	alkylenyl	heterocyclenyl	-C≡C-
128	alkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-C≡C-
129	cycloalkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-C≡C-
130	heterocyclenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-C≡C-
131	-	-C≡C-	alkylenyl	heterocyclenyl	-C≡C-
132	alkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-C≡C-
133	cycloalkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-C≡C-
134	heterocyclenyl	-C≡C-	alkylenyl	heterocyclenyl	-C≡C-
135	alkylenyl	-	heterocyclenyl	alkylenyl	-C≡C-
136	cycloalkylenyl	-	heterocyclenyl	alkylenyl	-C≡C-
137	heterocyclenyl	-	heterocyclenyl	alkylenyl	-C≡C-
138	-	-C(=O)-	heterocyclenyl	alkylenyl	-C≡C-
139	alkylenyl	-C(=O)-	heterocyclenyl	alkylenyl	-C≡C-
140	cycloalkylenyl	-C(=O)-	heterocyclenyl	alkylenyl	-C≡C-
141	heterocyclenyl	-C(=O)-	heterocyclenyl	alkylenyl	-C≡C-
142	-	-C(=O)NH-	heterocyclenyl	alkylenyl	-C≡C-
143	alkylenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-C≡C-
144	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-C≡C-
145	heterocyclenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-C≡C-
146	-	-C≡C-	heterocyclenyl	alkylenyl	-C≡C-
147	alkylenyl	-C≡C-	heterocyclenyl	alkylenyl	-C≡C-
148	cycloalkylenyl	-C≡C-	heterocyclenyl	alkylenyl	-C≡C-
149	heterocyclenyl	-C≡C-	heterocyclenyl	alkylenyl	-C≡C-
150	alkylenyl	-	-	cycloalkylenyl	-C≡C-
151	cycloalkylenyl	-	-	cycloalkylenyl	-C≡C-
152	heterocyclenyl	-	-	cycloalkylenyl	-C≡C-
153	-	-C(=O)-	-	cycloalkylenyl	-C≡C-
154	alkylenyl	-C(=O)-	-	cycloalkylenyl	-C≡C-

155	cycloalkylenyl	-C(=O)-	-	cycloalkylenyl	-C≡C-
156	heterocyclenyl	-C(=O)-	-	cycloalkylenyl	-C≡C-
157	-	-C(=O)NH-	-	cycloalkylenyl	-C≡C-
158	alkylenyl	-C(=O)NH-	-	cycloalkylenyl	-C≡C-
159	cycloalkylenyl	-C(=O)NH-	-	cycloalkylenyl	-C≡C-
160	heterocyclenyl	-C(=O)NH-	-	cycloalkylenyl	-C≡C-
161	-	-C≡C-	-	cycloalkylenyl	-C≡C-
162	alkylenyl	-C≡C-	-	cycloalkylenyl	-C≡C-
163	cycloalkylenyl	-C≡C-	-	cycloalkylenyl	-C≡C-
164	heterocyclenyl	-C≡C-	-	cycloalkylenyl	-C≡C-
165	alkylenyl	-	alkylenyl	cycloalkylenyl	-C≡C-
166	cycloalkylenyl	-	alkylenyl	cycloalkylenyl	-C≡C-
167	heterocyclenyl	-	alkylenyl	cycloalkylenyl	-C≡C-
168	-	-C(=O)-	alkylenyl	cycloalkylenyl	-C≡C-
169	alkylenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-C≡C-
170	cycloalkylenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-C≡C-
171	heterocyclenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-C≡C-
172	-	-C(=O)NH-	alkylenyl	cycloalkylenyl	-C≡C-
173	alkylenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-C≡C-
174	cycloalkylenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-C≡C-
175	heterocyclenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-C≡C-
176	-	-C≡C-	alkylenyl	cycloalkylenyl	-C≡C-
177	alkylenyl	-C≡C-	alkylenyl	cycloalkylenyl	-C≡C-
178	cycloalkylenyl	-C≡C-	alkylenyl	cycloalkylenyl	-C≡C-
179	heterocyclenyl	-C≡C-	alkylenyl	cycloalkylenyl	-C≡C-
180	alkylenyl	-	heterocyclenyl	cycloalkylenyl	-C≡C-
181	cycloalkylenyl	-	heterocyclenyl	cycloalkylenyl	-C≡C-
182	heterocyclenyl	-	heterocyclenyl	cycloalkylenyl	-C≡C-
183	-	-C(=O)-	heterocyclenyl	cycloalkylenyl	-C≡C-
184	alkylenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-C≡C-
185	cycloalkylenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-C≡C-
186	heterocyclenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-C≡C-
187	-	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-C≡C-

188	alkylenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-C≡C-
189	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-C≡C-
190	heterocyclenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-C≡C-
191	-	-C≡C-	heterocyclenyl	cycloalkylenyl	-C≡C-
192	alkylenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-C≡C-
193	cycloalkylenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-C≡C-
194	heterocyclenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-C≡C-
195	alkylenyl	-	-	-	-O-
196	cycloalkylenyl	-	-	-	-O-
197	heterocyclenyl	-	-	-	-O-
198	cycloalkylenyl	-	alkylenyl	-	-O-
199	heterocyclenyl	-	alkylenyl	-	-O-
200	-	-C(=O)-	alkylenyl	-	-O-
201	alkylenyl	-C(=O)-	alkylenyl	-	-O-
202	cycloalkylenyl	-C(=O)-	alkylenyl	-	-O-
203	heterocyclenyl	-C(=O)-	alkylenyl	-	-O-
204	-	-C(=O)NH-	alkylenyl	-	-O-
205	alkylenyl	-C(=O)NH-	alkylenyl	-	-O-
206	cycloalkylenyl	-C(=O)NH-	alkylenyl	-	-O-
207	heterocyclenyl	-C(=O)NH-	alkylenyl	-	-O-
208	-	-C≡C-	alkylenyl	-	-O-
209	alkylenyl	-C≡C-	alkylenyl	-	-O-
210	cycloalkylenyl	-C≡C-	alkylenyl	-	-O-
211	heterocyclenyl	-C≡C-	alkylenyl	-	-O-
212	alkylenyl	-	heterocyclenyl	-	-O-
213	cycloalkylenyl	-	heterocyclenyl	-	-O-
214	heterocyclenyl	-	heterocyclenyl	-	-O-
215	-	-C(=O)-	heterocyclenyl	-	-O-
216	alkylenyl	-C(=O)-	heterocyclenyl	-	-O-
217	cycloalkylenyl	-C(=O)-	heterocyclenyl	-	-O-
218	heterocyclenyl	-C(=O)-	heterocyclenyl	-	-O-
219	-	-C(=O)NH-	heterocyclenyl	-	-O-
220	alkylenyl	-C(=O)NH-	heterocyclenyl	-	-O-

221	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	-	-O-
222	heterocyclenyl	-C(=O)NH-	heterocyclenyl	-	-O-
223	-	-C≡C-	heterocyclenyl	-	-O-
224	alkylenyl	-C≡C-	heterocyclenyl	-	-O-
225	cycloalkylenyl	-C≡C-	heterocyclenyl	-	-O-
226	heterocyclenyl	-C≡C-	heterocyclenyl	-	-O-
227	alkylenyl	-	alkylenyl	heterocyclenyl	-O-
228	cycloalkylenyl	-	alkylenyl	heterocyclenyl	-O-
229	heterocyclenyl	-	alkylenyl	heterocyclenyl	-O-
230	-	-C(=O)-	alkylenyl	heterocyclenyl	-O-
231	alkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-O-
232	cycloalkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-O-
233	heterocyclenyl	-C(=O)-	alkylenyl	heterocyclenyl	-O-
234	-	-C(=O)NH-	alkylenyl	heterocyclenyl	-O-
235	alkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-O-
236	cycloalkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-O-
237	heterocyclenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-O-
238	-	-C≡C-	alkylenyl	heterocyclenyl	-O-
239	alkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-O-
240	cycloalkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-O-
241	heterocyclenyl	-C≡C-	alkylenyl	heterocyclenyl	-O-
242	alkylenyl	-	heterocyclenyl	alkylenyl	-O-
243	cycloalkylenyl	-	heterocyclenyl	alkylenyl	-O-
244	heterocyclenyl	-	heterocyclenyl	alkylenyl	-O-
245	-	-C(=O)-	heterocyclenyl	alkylenyl	-O-
246	alkylenyl	-C(=O)-	heterocyclenyl	alkylenyl	-O-
247	cycloalkylenyl	-C(=O)-	heterocyclenyl	alkylenyl	-O-
248	heterocyclenyl	-C(=O)-	heterocyclenyl	alkylenyl	-O-
249	-	-C(=O)NH-	heterocyclenyl	alkylenyl	-O-
250	alkylenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-O-
251	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-O-
252	heterocyclenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-O-
253	-	-C≡C-	heterocyclenyl	alkylenyl	-O-

254	alkylenyl	-C≡C-	heterocyclenyl	alkylenyl	-O-
255	cycloalkylenyl	-C≡C-	heterocyclenyl	alkylenyl	-O-
256	heterocyclenyl	-C≡C-	heterocyclenyl	alkylenyl	-O-
257	alkylenyl	-	-	cycloalkylenyl	-O-
258	cycloalkylenyl	-	-	cycloalkylenyl	-O-
259	heterocyclenyl	-	-	cycloalkylenyl	-O-
260	-	-C(=O)-	-	cycloalkylenyl	-O-
261	alkylenyl	-C(=O)-	-	cycloalkylenyl	-O-
262	cycloalkylenyl	-C(=O)-	-	cycloalkylenyl	-O-
263	heterocyclenyl	-C(=O)-	-	cycloalkylenyl	-O-
264	-	-C(=O)NH-	-	cycloalkylenyl	-O-
265	alkylenyl	-C(=O)NH-	-	cycloalkylenyl	-O-
266	cycloalkylenyl	-C(=O)NH-	-	cycloalkylenyl	-O-
267	heterocyclenyl	-C(=O)NH-	-	cycloalkylenyl	-O-
268	-	-C≡C-	-	cycloalkylenyl	-O-
269	alkylenyl	-C≡C-	-	cycloalkylenyl	-O-
270	cycloalkylenyl	-C≡C-	-	cycloalkylenyl	-O-
271	heterocyclenyl	-C≡C-	-	cycloalkylenyl	-O-
272	alkylenyl	-	alkylenyl	cycloalkylenyl	-O-
273	cycloalkylenyl	-	alkylenyl	cycloalkylenyl	-O-
274	heterocyclenyl	-	alkylenyl	cycloalkylenyl	-O-
275	-	-C(=O)-	alkylenyl	cycloalkylenyl	-O-
276	alkylenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-O-
277	cycloalkylenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-O-
278	heterocyclenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-O-
279	-	-C(=O)NH-	alkylenyl	cycloalkylenyl	-O-
280	alkylenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-O-
281	cycloalkylenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-O-
282	heterocyclenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-O-
283	-	-C≡C-	alkylenyl	cycloalkylenyl	-O-
284	alkylenyl	-C≡C-	alkylenyl	cycloalkylenyl	-O-
285	cycloalkylenyl	-C≡C-	alkylenyl	cycloalkylenyl	-O-
286	heterocyclenyl	-C≡C-	alkylenyl	cycloalkylenyl	-O-

287	alkylenyl	-	heterocyclenyl	cycloalkylenyl	-O-
288	cycloalkylenyl	-	heterocyclenyl	cycloalkylenyl	-O-
289	heterocyclenyl	-	heterocyclenyl	cycloalkylenyl	-O-
290	-	-C(=O)-	heterocyclenyl	cycloalkylenyl	-O-
291	alkylenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-O-
292	cycloalkylenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-O-
293	heterocyclenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-O-
294	-	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-O-
295	alkylenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-O-
296	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-O-
297	heterocyclenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-O-
298	-	-C≡C-	heterocyclenyl	cycloalkylenyl	-O-
299	alkylenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-O-
300	cycloalkylenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-O-
301	heterocyclenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-O-
302	alkylenyl	-	-	-	-NH-
303	cycloalkylenyl	-	-	-	-NH-
304	heterocyclenyl	-	-	-	-NH-
305	cycloalkylenyl	-	alkylenyl	-	-NH-
306	heterocyclenyl	-	alkylenyl	-	-NH-
307	-	-C(=O)-	alkylenyl	-	-NH-
308	alkylenyl	-C(=O)-	alkylenyl	-	-NH-
309	cycloalkylenyl	-C(=O)-	alkylenyl	-	-NH-
310	heterocyclenyl	-C(=O)-	alkylenyl	-	-NH-
311	-	-C(=O)NH-	alkylenyl	-	-NH-
312	alkylenyl	-C(=O)NH-	alkylenyl	-	-NH-
313	cycloalkylenyl	-C(=O)NH-	alkylenyl	-	-NH-
314	heterocyclenyl	-C(=O)NH-	alkylenyl	-	-NH-
315	-	-C≡C-	alkylenyl	-	-NH-
316	alkylenyl	-C≡C-	alkylenyl	-	-NH-
317	cycloalkylenyl	-C≡C-	alkylenyl	-	-NH-
318	heterocyclenyl	-C≡C-	alkylenyl	-	-NH-
319	alkylenyl	-	heterocyclenyl	-	-NH-

320	cycloalkylenyl	-	heterocyclenyl	-	-NH-
321	heterocyclenyl	-	heterocyclenyl	-	-NH-
322	-	-C(=O)-	heterocyclenyl	-	-NH-
323	alkylenyl	-C(=O)-	heterocyclenyl	-	-NH-
324	cycloalkylenyl	-C(=O)-	heterocyclenyl	-	-NH-
325	heterocyclenyl	-C(=O)-	heterocyclenyl	-	-NH-
326	-	-C(=O)NH-	heterocyclenyl	-	-NH-
327	alkylenyl	-C(=O)NH-	heterocyclenyl	-	-NH-
328	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	-	-NH-
329	heterocyclenyl	-C(=O)NH-	heterocyclenyl	-	-NH-
330	-	-C≡C-	heterocyclenyl	-	-NH-
331	alkylenyl	-C≡C-	heterocyclenyl	-	-NH-
332	cycloalkylenyl	-C≡C-	heterocyclenyl	-	-NH-
333	heterocyclenyl	-C≡C-	heterocyclenyl	-	-NH-
334	alkylenyl	-	alkylenyl	heterocyclenyl	-NH-
335	cycloalkylenyl	-	alkylenyl	heterocyclenyl	-NH-
336	heterocyclenyl	-	alkylenyl	heterocyclenyl	-NH-
337	-	-C(=O)-	alkylenyl	heterocyclenyl	-NH-
338	alkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-NH-
339	cycloalkylenyl	-C(=O)-	alkylenyl	heterocyclenyl	-NH-
340	heterocyclenyl	-C(=O)-	alkylenyl	heterocyclenyl	-NH-
341	-	-C(=O)NH-	alkylenyl	heterocyclenyl	-NH-
342	alkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-NH-
343	cycloalkylenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-NH-
344	heterocyclenyl	-C(=O)NH-	alkylenyl	heterocyclenyl	-NH-
345	-	-C≡C-	alkylenyl	heterocyclenyl	-NH-
346	alkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-NH-
347	cycloalkylenyl	-C≡C-	alkylenyl	heterocyclenyl	-NH-
348	heterocyclenyl	-C≡C-	alkylenyl	heterocyclenyl	-NH-
349	alkylenyl	-	heterocyclenyl	alkylenyl	-NH-
350	cycloalkylenyl	-	heterocyclenyl	alkylenyl	-NH-
351	heterocyclenyl	-	heterocyclenyl	alkylenyl	-NH-
352	-	-C(=O)-	heterocyclenyl	alkylenyl	-NH-

353	alkylenyl	-C(=O)-	heterocyclenyl	alkylenyl	-NH-
354	cycloalkylenyl	-C(=O)-	heterocyclenyl	alkylenyl	-NH-
355	heterocyclenyl	-C(=O)-	heterocyclenyl	alkylenyl	-NH-
356	-	-C(=O)NH-	heterocyclenyl	alkylenyl	-NH-
357	alkylenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-NH-
358	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-NH-
359	heterocyclenyl	-C(=O)NH-	heterocyclenyl	alkylenyl	-NH-
360	-	-C≡C-	heterocyclenyl	alkylenyl	-NH-
361	alkylenyl	-C≡C-	heterocyclenyl	alkylenyl	-NH-
362	cycloalkylenyl	-C≡C-	heterocyclenyl	alkylenyl	-NH-
363	heterocyclenyl	-C≡C-	heterocyclenyl	alkylenyl	-NH-
364	alkylenyl	-	-	cycloalkylenyl	-NH-
365	cycloalkylenyl	-	-	cycloalkylenyl	-NH-
366	heterocyclenyl	-	-	cycloalkylenyl	-NH-
367	-	-C(=O)-	-	cycloalkylenyl	-NH-
368	alkylenyl	-C(=O)-	-	cycloalkylenyl	-NH-
369	cycloalkylenyl	-C(=O)-	-	cycloalkylenyl	-NH-
370	heterocyclenyl	-C(=O)-	-	cycloalkylenyl	-NH-
371	-	-C(=O)NH-	-	cycloalkylenyl	-NH-
372	alkylenyl	-C(=O)NH-	-	cycloalkylenyl	-NH-
373	cycloalkylenyl	-C(=O)NH-	-	cycloalkylenyl	-NH-
374	heterocyclenyl	-C(=O)NH-	-	cycloalkylenyl	-NH-
375	-	-C≡C-	-	cycloalkylenyl	-NH-
376	alkylenyl	-C≡C-	-	cycloalkylenyl	-NH-
377	cycloalkylenyl	-C≡C-	-	cycloalkylenyl	-NH-
378	heterocyclenyl	-C≡C-	-	cycloalkylenyl	-NH-
379	alkylenyl	-	alkylenyl	cycloalkylenyl	-NH-
380	cycloalkylenyl	-	alkylenyl	cycloalkylenyl	-NH-
381	heterocyclenyl	-	alkylenyl	cycloalkylenyl	-NH-
382	-	-C(=O)-	alkylenyl	cycloalkylenyl	-NH-
383	alkylenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-NH-
384	cycloalkylenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-NH-
385	heterocyclenyl	-C(=O)-	alkylenyl	cycloalkylenyl	-NH-

386	-	-C(=O)NH-	alkylenyl	cycloalkylenyl	-NH-
387	alkylenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-NH-
388	cycloalkylenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-NH-
389	heterocyclenyl	-C(=O)NH-	alkylenyl	cycloalkylenyl	-NH-
390	-	-C≡C-	alkylenyl	cycloalkylenyl	-NH-
391	alkylenyl	-C≡C-	alkylenyl	cycloalkylenyl	-NH-
392	cycloalkylenyl	-C≡C-	alkylenyl	cycloalkylenyl	-NH-
393	heterocyclenyl	-C≡C-	alkylenyl	cycloalkylenyl	-NH-
394	alkylenyl	-	heterocyclenyl	cycloalkylenyl	-NH-
395	cycloalkylenyl	-	heterocyclenyl	cycloalkylenyl	-NH-
396	heterocyclenyl	-	heterocyclenyl	cycloalkylenyl	-NH-
397	-	-C(=O)-	heterocyclenyl	cycloalkylenyl	-NH-
398	alkylenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-NH-
399	cycloalkylenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-NH-
400	heterocyclenyl	-C(=O)-	heterocyclenyl	cycloalkylenyl	-NH-
401	-	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-NH-
402	alkylenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-NH-
403	cycloalkylenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-NH-
404	heterocyclenyl	-C(=O)NH-	heterocyclenyl	cycloalkylenyl	-NH-
405	-	-C≡C-	heterocyclenyl	cycloalkylenyl	-NH-
406	alkylenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-NH-
407	cycloalkylenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-NH-
408	heterocyclenyl	-C≡C-	heterocyclenyl	cycloalkylenyl	-NH-

[0400] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIII-XXXIV**, or a pharmaceutically acceptable salt or solvate thereof, wherein Q is a small molecule that binds to a target protein of interest.

[0401] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIII-XXXIV**, or a pharmaceutically acceptable salt or solvate thereof, wherein Q is a Hsp90 inhibitor, a kinase inhibitor, a MDM2 inhibitor, a compound targeting cytosolic signaling protein, a HDAC inhibitor, a human lysine methyltransferase inhibitor, an angiogenesis inhibitor, an immunosuppressive compound, or compound a targeting the aryl hydrocarbon receptor (AHR).

[0402] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIII-XXXIV**, or a pharmaceutically acceptable salt or solvate thereof, wherein Q binds to a kinase, a cytosolic signaling protein, e.g., FKBP12, a nuclear protein, a histone deacetylase, a lysine methyltransferase, a protein regulating angiogenesis, a protein regulating immune response, an aryl hydrocarbon receptor (AHR), a glucocorticoid receptor, or a transcription factor, e.g., SMARCA4, SMARCA2, TRIM24.

[0403] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIII-XXXIV**, or a pharmaceutically acceptable salt or solvate thereof, wherein Q binds to a kinase, e.g., a tyrosine kinase, e.g., AATK, ABL, ABL2, ALK, AXL, BLK, BMX, BTK, CSF1R, CSK, DDR1, DDR2, EGFR, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, ERBB2, ERBB3, ERBB4, FER, FES, FGFR1, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT3, FLT4, FRK, FYN, GSG2, HCK, IGF1R, ILK, INSR, INSRR, IRAK4, ITK, JAK1, JAK2, JAK3, KDR, KIT, KSR1, LCK, LMTK2, LMTK3, LTK, LYN, MATK, MERTK, MET, MLTK, MST1R, MUSK, NPR1, NTRK1, NTRK2, NTRK3, PDGFRA, PDGFRB, PLK4, PTK2, PTK2B, PTK6, PTK7, RET, ROR1, ROR2, ROS1, RYK, SGK493, SRC, SRMS, STYK1, SYK, TEC, TEK, TEX14, TIE1, TNK1, TNK2, TNNI3K, TXK, TYK2, TYRO3, YES1, or ZAP70; a aserine/threonine kinase, e.g., casein kinase 2, protein kinase A, protein kinase B, protein kinase C, Raf kinases, CaM kinases, AKT1, AKT2, AKT3, ALK1, ALK2, ALK3, ALK4, Aurora A, Aurora B, Aurora C, CHK1, CHK2, CLK1, CLK2, CLK3, DAPK1, DAPK2, DAPK3, DMPK, ERK1, ERK2, ERK5, GCK, GSK3, HIPK, KHS1, LKB1, LOK, MAPKAPK2, MAPKAPK, MNK1, MSSK1, MST1, MST2, MST4, NDR,NEK2, NEK3, NEK6, NEK7, NEK9, NEK11, PAK1, PAK2, PAK3, PAK4, PAK5, PAK6, PIM1, PIM2, PLK1, RIP2, RIP5, RSK1, RSK2, SGK2, SGK3, SIK1, STK33, TAO1, TAO2, TGF-beta, TLK2, TSSK1, TSSK2, ULK1, or ULK2; a cyclin dependent kinase, e.g., Cdk1-Cdk11, or a leucine-rich repeat kinase, e.g., LRRK2.

[0404] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIII-XXXIV**, or a pharmaceutically acceptable salt or solvate thereof, wherein Q binds to antennapedia homeodomain protein, BRCA1, BRCA2, CCAAT-enhanced-binding proteins, histones, polycomb-group proteins, high mobility group proteins, telomere binding proteins, FANCA, FANCD2, FANCE, FANCF, hepatocyte

nuclear factors, Mad2, NF-kappa B, nuclear receptor coactivators, CREB-binding protein, p55, p107, p130, Rb proteins, p53, c-fos, c-jun, c-mdm2, c-myc, or c-rel.

[0405] In another embodiment, PROTAC Molecules are compounds of any one of Formulae **XXIII-XXXIV**, or a pharmaceutically acceptable salt or solvate thereof, wherein Q is a half-life extending moiety, *see, e.g.,* Bech et al., *ASC Med. Chem. Lett. 9*:577-580 (2018), a fluorophore, or a dye.

VII. Definitions

[0406] The term "a disease or condition wherein inhibition of CRBN ubiquitination provides a benefit" and the like pertains to a disease or condition in which CRBN ubiquitination is important or necessary, e.g., for the onset, progress, expression of that disease or condition, or a disease or a condition which is known to be treated by an CRBN ubiquitination inhibitor, e.g., thalidomide, lenalidomide, pomalidomide, and related analogs. Examples of such conditions include, but are not limited, cancer. One of ordinary skill in the art is readily able to determine whether a compound treats a disease or condition mediated by a CRBN ubiquitination inhibitor for any particular cell type, for example, by assays which conveniently can be used to assess the activity of particular compounds.

[0407] The terms "cereblon" or "CRBN" refers to a protein that is encoded by the CRBN gene in humans. Cereblon forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1), Cullin-4A (CUL4A), and regulator of cullins 1 (ROC1). This complex ubiquitinates a number of other proteins. Angers et al., *Nature 443*:590-593 (2006)

[0408] The term "optional therapeutic agent" refers to a therapeutic agent different from a Compound of the Disclosure and that is known to treat the disease or condition of interest. For example when a cancer is the disease or condition of interest, the optional therapeutic agent can be a known chemotherapeutic drug, like taxol, or radiation, for example.

[0409] The term "disease" or “condition” denotes disturbances and/or anomalies that as a rule are regarded as being pathological conditions or functions, and that can manifest themselves in the form of particular signs, symptoms, and/or malfunctions. Compounds of the Disclosure are inhibitors of CRBN ubiquitination and can be used in treating or preventing diseases and conditions wherein the inhibition of CRBN ubiquitination provides a benefit.

[0410] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such treatment. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.

[0411] As used herein, the terms "prevent," "preventing," and "prevention" refer to a method of preventing the onset of a disease or condition and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent," "preventing," and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease. The terms "prevent," "preventing" and "prevention" may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition.

[0412] The term "therapeutically effective amount" or "effective dose" as used herein refers to an amount of the active ingredient(s) that is(are) sufficient, when administered by a method of the disclosure, to efficaciously deliver the active ingredient(s) for the treatment of condition or disease of interest to a subject in need thereof. In the case of a cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (i.e., retard to some extent or stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., retard to some extent or stop) cancer cell infiltration into peripheral organs; inhibit (i.e., retard to some extent or stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve, to some extent, one or more of the symptoms associated with the cancer. To the extent the administered compound or composition prevents growth and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic.

[0413] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0414] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and subject to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0415] "Concurrent administration," "administered in combination," "simultaneous administration," and similar phrases mean that two or more agents are administered concurrently to the subject being treated. By "concurrently," it is meant that each agent is administered either simultaneously or sequentially in any order at different points in time. However, if not administered simultaneously, it is meant that they are administered to a subject in a sequence and sufficiently close in time so as to provide the desired therapeutic effect and can act in concert. For example, a Compound of the Disclosure can be administered at the same time or sequentially in any order at different points in time as an optional therapeutic agent. A Compound of the Disclosure and the optional therapeutic agent can be administered separately, in any appropriate form and by any suitable route. When a Compound of the Disclosure and the optional therapeutic agent are not administered concurrently, it is understood that they can be administered in any order to a subject in need thereof. For example, a Compound of the Disclosure can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of an optional therapeutic agent treatment modality (e.g., radiotherapy), to a subject in need thereof. In various embodiments, a Compound of the Disclosure and the optional therapeutic agent are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In one embodiment, the components of the combination therapies are administered at about 1 minute to about 24 hours apart.

[0416] The use of the terms "a", "an", "the", and similar referents in the context of describing the disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended to better illustrate the disclosure and is not a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

[0417] The term "halo" as used herein by itself or as part of another group refers to -Cl, -F, -Br, or -I.

[0418] The term "nitro" as used herein by itself or as part of another group refers to $-NO_2$.

[0419] The term "cyano" as used herein by itself or as part of another group refers to -CN.

[0420] The term "hydroxy" as herein used by itself or as part of another group refers to -OH.

[0421] The term "alkyl" as used herein by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms, i.e., a C_1-C_{12} alkyl, or the number of carbon atoms designated, e.g., a C_1 alkyl such as methyl, a C_2 alkyl such as ethyl, etc. In one embodiment, the alkyl is a C_1-C_{10} alkyl. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl is a C_1-C_3 alkyl, i.e., methyl, ethyl, propyl, or isopropyl. Non-limiting exemplary C_1-C_{12} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl.

[0422] The term "optionally substituted alkyl" as used herein by itself or as part of another group refers to an alkyl group that is either unsubstituted or substituted with one, two, or three substituents, wherein each substituent is independently nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carbamate, carboxy, alkoxycarbonyl,

carboxyalkyl, $-N(R^{50a})C(=O)R^{50b}$, $-N(R^{50a})S(=O)_2R^{50c}$, $-C(=O)R^{51}$, $-S(=O)R^{52}$, or $-S(=O)_2R^{53}$; wherein:

[0423] R^{50a} is hydrogen or alkyl;

[0424] R^{50b} is alkyl, haloalkyl, optionally substituted cycloalkyl, alkoxy, (alkoxy)alkyl, (aryl)alkyl, (heteroaryl)alkyl, (amino)alkyl, (hydroxy)alkyl, (cyano)alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycle, optionally substituted C_6-C_{10} aryl, or optionally substituted heteroaryl;

[0425] R^{50c} is alkyl, haloalkyl, optionally substituted cycloalkyl, (alkoxy)alkyl, (aryl)alkyl, (heteroaryl)alkyl, (amino)alkyl, (hydroxy)alkyl, (cyano)alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycle, optionally substituted C_6-C_{10} aryl, or optionally substituted heteroaryl;

[0426] R^{51} is haloalkyl, optionally substituted cycloalkyl, alkoxy, (alkoxy)alkyl, (aryl)alkyl, (heteroaryl)alkyl, (amino)alkyl, (hydroxy)alkyl, (cyano)alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycle, or optionally substituted heteroaryl;

[0427] R^{52} is alkyl, haloalkyl, optionally substituted cycloalkyl, alkoxy, (alkoxy)alkyl, (aryl)alkyl, (heteroaryl)alkyl, (amino)alkyl, (hydroxy)alkyl, (cyano)alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycle, optionally substituted C_6-C_{10} aryl, or optionally substituted heteroaryl; and

[0428] R^{53} is haloalkyl, optionally substituted cycloalkyl, alkoxy, (alkoxy)alkyl, (aryl)alkyl, (heteroaryl)alkyl, (amino)alkyl, (hydroxy)alkyl, (cyano)alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycle, or optionally substituted heteroaryl. Non-limiting exemplary optionally substituted alkyl groups include $-CH(CO_2Me)CH_2CO_2Me$ and $-CH(CH_3)CH_2N(H)C(=O)O(CH_3)_3$.

[0429] The term "alkenyl" as used herein by itself or as part of another group refers to an alkyl group containing one, two, or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is a C_2-C_6 alkenyl group. In another embodiment, the alkenyl group is a C_2-C_4 alkenyl group. In another embodiment, the alkenyl group has one carbon-to-carbon double bond. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

[0430] The term "optionally substituted alkenyl" as used herein by itself or as part of another refers to an alkenyl group that is either unsubstituted or substituted with one, two or three substituents, wherein each substituent is independently halo, nitro, cyano, hydroxy, amino (e.g., alkylamino, dialkylamino), haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclo. Non-limiting exemplary optionally substituted alkenyl groups include -CH=CHPh.

[0431] The term "alkynyl" as used herein by itself or as part of another group refers to an alkyl group containing one, two, or three carbon-to-carbon triple bonds. In one embodiment, the alkynyl is a C_2-C_6 alkynyl. In another embodiment, the alkynyl is a C_2-C_4 alkynyl. In another embodiment, the alkynyl has one carbon-to-carbon triple bond. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[0432] The term "optionally substituted alkynyl" as used herein by itself or as part of another group refers to an alkynyl group that is either unsubstituted or substituted with one, two or three substituents, wherein each substituent is independently halo, nitro, cyano, hydroxy, amino, e.g., alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclo. Non-limiting exemplary optionally substituted alkynyl groups include -C≡CPh and -CH(Ph)C≡CH.

[0433] The term "haloalkyl" as used herein by itself or as part of another group refers to an alkyl group substituted by one or more fluorine, chlorine, bromine, and/or iodine atoms. In one embodiment, the alkyl is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the alkyl is substituted by one, two, or three fluorine atoms. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl group is a C_1 or C_2 alkyl. Non-limiting exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

[0434] The terms "hydroxyalkyl" or "(hydroxy)alkyl" as used herein by themselves or as part of another group refer to an alkyl group substituted with one, two, or three hydroxy groups. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl is a C_1 or C_2 alkyl. In another embodiment, the hydroxyalkyl is a monohydroxyalkyl group, i.e., substituted with one hydroxy group. In another embodiment, the hydroxyalkyl group is a dihydroxyalkyl group, i.e., substituted with two hydroxy groups. Non-limiting exemplary (hydroxyl)alkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

[0435] The term "alkoxy" as used herein by itself or as part of another group refers to an alkyl group or alkenyl group attached to a terminal oxygen atom. In one embodiment, the alkyl is a C_1-C_6 alkyl and resulting alkoxy is thus referred to as a "C_1-C_6 alkoxy." In another embodiment, the alkyl is a C_1-C_4 alkyl group. Non-limiting exemplary alkoxy groups include methoxy, ethoxy, and *tert*-butoxy.

[0436] The term "haloalkoxy" as used herein by itself or as part of another group refers to a haloalkyl group attached to a terminal oxygen atom. In one embodiment, the haloalkyl group is a C_1-C_6 haloalkyl. In another embodiment, the haloalkyl group is a C_1-C_4 haloalkyl group. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

[0437] The term "alkylthio" as used herein by itself or as part of another group refers to an alkyl group attached to a terminal sulfur atom. In one embodiment, the alkyl group is a C_1-C_4 alkyl group. Non-limiting exemplary alkylthio groups include -SCH_3, and -SCH_2CH_3.

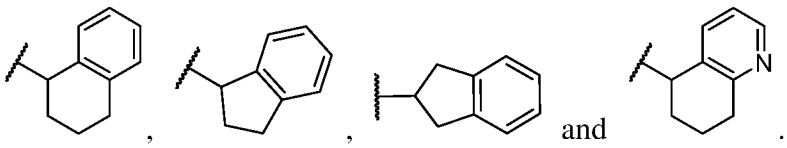
[0438] The terms "alkoxyalkyl" or "(alkoxy)alkyl" as used herein by themselves or as part of another group refers to an alkyl group substituted with one alkoxy group. In one embodiment, the alkoxy is a C_1-C_6 alkoxy. In another embodiment, the alkoxy is a C_1-C_4 alkoxy. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl.

[0439] The term "heteroalkyl" as used by itself or part of another group refers to unsubstituted straight- or branched-chain aliphatic hydrocarbons containing from three to twenty chain atoms, i.e., 3- to 20-membered heteroalkyl, or the number of chain atoms designated, wherein at least one $-CH_2-$ is replaced with at least one of -O-, -N(H)-, -N(C_1-C_4 alkyl)-, or -S-. The - O-, -N(H)-, -N(C_1-C_4 alkyl)-, or -S- can independently be placed at any interior position of the aliphatic hydrocarbon chain so long as each -O-, -N(H)-, -N(C_1-C_4 alkyl)-, and -S- group is separated by at least two $-CH_2-$ groups. In one embodiment, one $-CH_2-$ group is replaced with one -O- group. In another embodiment, two $-CH_2-$ groups are replaced with two -O- groups. In another embodiment, three $-CH_2-$ groups are replaced with three -O- groups. In another embodiment, four $-CH_2-$ groups are replaced with four -O- groups. Non-limiting exemplary heteroalkyl groups include $-CH_2OCH_3$, $-CH_2OCH_2CH_2CH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_3$.

[0440] The term "cycloalkyl" as used herein by itself or as part of another group refers to saturated and partially unsaturated, e.g., containing one or two double bonds, monocyclic, bicyclic, or tricyclic aliphatic hydrocarbons containing three to twelve carbon atoms, i.e., a C_{3-12} cycloalkyl, or the number of carbons designated, e.g., a C_3 cycloalkyl such a cyclopropyl, a C_4 cycloalkyl such as cyclobutyl, etc. In one embodiment, the cycloalkyl is bicyclic, i.e., it has two rings. In another embodiment, the cycloalkyl is monocyclic, i.e., it has one ring. In another embodiment, the cycloalkyl is a C_{3-8} cycloalkyl. In another embodiment, the cycloalkyl is a C_{3-6} cycloalkyl, i.e., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In another embodiment, the cycloalkyl is a C_5 cycloalkyl, i.e., cyclopentyl. In another embodiment, the cycloalkyl is a C_6 cycloalkyl, i.e., cyclohexyl. Non-limiting exemplary C_{3-12} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, and spiro[3.3]heptane.

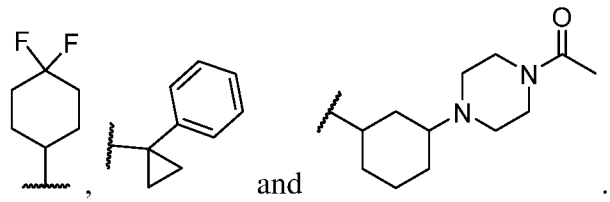
[0441] The term "optionally substituted cycloalkyl" as used herein by itself or as part of another group refers to a cycloalkyl group that is either unsubstituted or substituted with one, two, or three substituents, wherein each substituent is independently halo, nitro, cyano, hydroxy, amino (e.g., $-NH_2$, alkylamino, dialkylamino, aralkylamino, hydroxyalkylamino, or (heterocyclo)alkylamino), heteroalkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl,

alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, $-N(R^{50a})C(=O)R^{50b}$,$-N(R^{50a})S(=O)_2R^{50c}$, $-C(=O)R^{51}$, $-S(=O)R^{52}$, $-S(=O)_2R^{53}$, or $-OR^{54}$, wherein R^{50a}, R^{50b}, R^{50c}, R^{52}, R^{51}, and R^{53} are as defined in connection with the term "optionally substituted alkyl" and R^{54} is (hydroxy)alkyl or (amino)alkyl. The term optionally substituted cycloalkyl also includes cycloalkyl groups having fused optionally substituted aryl or optionally substituted heteroaryl groups such as



and .

[0442] Non-limiting exemplary optionally substituted cycloalkyl groups include:



and .

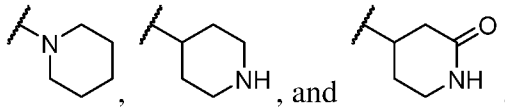
[0443] The term "heterocyclo" as used herein by itself or as part of another group refers to saturated and partially unsaturated, e.g., containing one or two double bonds, monocyclic, bicyclic, or tricyclic groups containing three to fourteen ring members, i.e., a 3- to 14-membered heterocyclo, comprising one, two, three, or four heteroatoms. Each heteroatom is independently oxygen, sulfur, or nitrogen. Each sulfur atom is independently oxidized to give a sulfoxide, i.e., S(=O), or sulfone, i.e., $S(=O)_2$.

[0444] The term heterocyclo includes groups wherein one or more $-CH_2-$ groups is replaced with one or more -C(=O)- groups, including cyclic ureido groups such as imidazolidinyl-2-one, cyclic amide groups such as pyrrolidin-2-one or piperidin-2-one, and cyclic carbamate groups such as oxazolidinyl-2-one.

[0445] The term heterocyclo also includes groups having fused optionally substituted aryl or optionally substituted heteroaryl groups such as indoline, indolin-2-one, 2,3-dihydro-1H-pyrrolo[2,3-c]pyridine, 2,3,4,5-tetrahydro-1H-benzo[d]azepine, or 1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one.

[0446] In one embodiment, the heterocyclo group is a 4- to 8-membered cyclic group containing one ring and one or two oxygen atoms, e.g., tetrahydrofuran or tetrahydropyran, or one or two nitrogen atoms, e.g., pyrrolidine, piperidine, or piperazine,

or one oxygen and one nitrogen atom, e.g., morpholine, and, optionally, one -CH_2- group is replaced with one -C(=O)- group, e.g., pyrrolidin-2-one or piperazin-2-one. In another embodiment, the heterocyclo group is a 5- to 8-membered cyclic group containing one ring and one or two nitrogen atoms and, optionally, one -CH_2- group is replaced with one -C(=O)- group. In another embodiment, the heterocyclo group is a 5- or 6-membered cyclic group containing one ring and one or two nitrogen atoms and, optionally, one -CH_2- group is replaced with one -C(=O)- group. In another embodiment, the heterocyclo group is a 8- to12-membered cyclic group containing two rings and one or two nitrogen atoms. The heterocyclo can be linked to the rest of the molecule through any available carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include:



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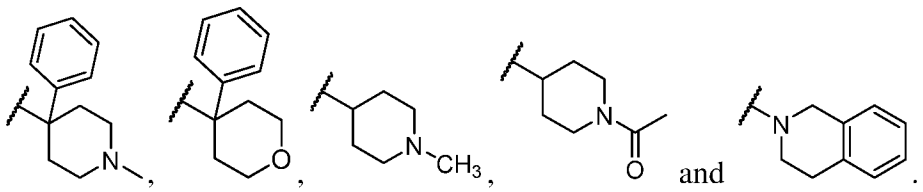
[0447] The term "optionally substituted heterocyclo" as used herein by itself or part of another group refers to a heterocyclo group that is either unsubstituted or substituted with one to four substituents, wherein each substituent is independently halo, nitro, cyano, hydroxy, amino, (e.g., -NH_2, alkylamino, dialkylamino, aralkylamino, hydroxyalkylamino, or (heterocyclo)alkylamino), heteroalkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, -$N(R^{50a})C(=O)R^{50b}$, -$N(R^{50a})S(=O)_2R^{50c}$, -$C(=O)R^{51}$, -$S(=O)R^{52}$, -$S(=O)_2R^{53}$, or -OR^{54}, wherein R^{50a}, R^{50b}, R^{50c}, R^{52}, R^{51}, R^{53}, and R^{54} are as defined in connection with the term "optionally substituted cycloalkyl." Substitution may occur on any available carbon or nitrogen atom of the heterocyclo group. Non-limiting exemplary optionally substituted heterocyclo groups include:



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[0448] The term "aryl" as used herein by itself or as part of another group refers to an aromatic ring system having six to fourteen carbon atoms, i.e., C_6-C_{14} aryl. Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is phenyl or naphthyl. In another embodiment, the aryl group is phenyl.

[0449] The term "optionally substituted aryl" as used herein by itself or as part of another group refers to aryl that is either unsubstituted or substituted with one to five substituents, wherein the substituents are each independently halo, nitro, cyano, hydroxy, amino, (e.g., $-NH_2$, alkylamino, dialkylamino, aralkylamino, hydroxyalkylamino, or (heterocyclo)alkylamino), heteroalkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, $-N(R^{50a})C(=O)R^{50b}$, $-N(R^{50a})S(=O)_2R^{50c}$, $-C(=O)R^{51}$, $-S(=O)R^{52}$, $-S(=O)_2R^{53}$, or $-OR^{54}$, wherein R^{50a}, R^{50b}, R^{50c}, R^{52}, R^{51}, R^{53}, and R^{54} are as defined in connection with the term "optionally substituted cycloalkyl."

[0450] In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In another embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. Non-limiting exemplary optionally substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, 3-chloro-4-fluorophenyl, and 2-phenylpropan-2-amine. The term optionally substituted aryl includes aryl groups having fused optionally substituted cycloalkyl groups and fused optionally substituted heterocyclo groups. Non-limiting xamples include: 2,3-dihydro-1H-inden-1-yl, 1,2,3,4-tetrahydronaphthalen-1-yl, 1,3,4,5-tetrahydro-2H-benzo[c]azepin-

2-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, and 2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl.

[0451] The term "heteroaryl" as used herein by itself or as part of another group refers to monocyclic and bicyclic aromatic ring systems having five to 14 fourteen ring members, i.e., a 5- to 14-membered heteroaryl, comprising one, two, three, or four heteroatoms. Each heteroatom is independently oxygen, sulfur, or nitrogen. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In another embodiment, the heteroaryl is a 5- to 10-membered heteroaryl. In another embodiment, the heteroaryl has 5 ring atoms, e.g., thienyl, a 5-membered heteroaryl having four carbon atoms and one sulfur atom. In another embodiment, the heteroaryl has 6 ring atoms, e.g., pyridyl, a 6-membered heteroaryl having five carbon atoms and one nitrogen atom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is chosen from thienyl (e.g., thien-2-yl and thien-3-yl), furyl (e.g., 2-furyl and 3-furyl), pyrrolyl (e.g., 1H-pyrrol-2-yl and 1H-pyrrol-3-yl), imidazolyl (e.g., 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (e.g., 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-yl), pyridyl (e.g., pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (e.g., pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (e.g., thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (e.g., isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (e.g., oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (e.g., isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl). The term heteroaryl also includes N-oxides. A non-limiting exemplary N-oxide is pyridyl N-oxide.

[0452] The term "optionally substituted heteroaryl" as used herein by itself or as part of another group refers to a heteroaryl that is either unsubstituted or substituted with one to four substituents, wherein the substituents are independently halo, nitro, cyano, hydroxy, amino, (e.g., -NH_2, alkylamino, dialkylamino, aralkylamino, hydroxyalkylamino, or (heterocyclo)alkylamino), heteroalkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy,

aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, $-N(R^{50a})C(=O)R^{50b}$, $-N(R^{50a})S(=O)_2R^{50c}$, $-C(=O)R^{51}$, $-S(=O)R^{52}$, $-S(=O)_2R^{53}$, or $-OR^{54}$, wherein R^{50a}, R^{50b}, R^{50c}, R^{52}, R^{51}, R^{53}, and R^{54} are as defined in connection with the term "optionally substituted cycloalkyl."

[0453] In one embodiment, the optionally substituted heteroaryl has two substituents. In another embodiment, the optionally substituted heteroaryl has one substituent. Any available carbon or nitrogen atom can be substituted.

[0454] The term "aryloxy" as used herein by itself or as part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is PhO-.

[0455] The term "heteroaryloxy" as used herein by itself or as part of another group refers to an optionally substituted heteroaryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is pyridyl-O-.

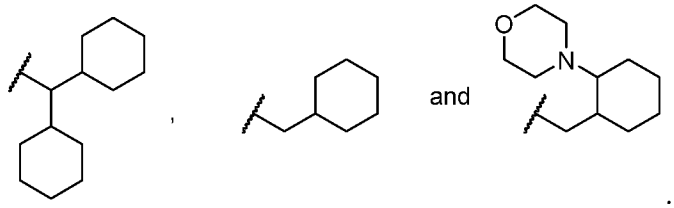
[0456] The term "aralkyloxy" as used herein by itself or as part of another group refers to an aralkyl attached to a terminal oxygen atom. A non-limiting exemplary aralkyloxy group is $PhCH_2O$-.

[0457] The term "carboxyalkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one carboxy group. In another embodiment, the alkyl is a C_1-C_4 alkyl. Non-limiting exemplary carboxyalkyl groups include $-CH_2CO_2H$ and $-CH_2CH_2CO_2H$.

[0458] The term "(cyano)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one, two, or three cyano groups. In one embodiment, the alkyl is substituted with one cyano group. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. Non-limiting exemplary (cyano)alkyl groups include $-CH_2CH_2CN$ and $-CH_2CH_2CH_2CN$.

[0459] The term "(cycloalkyl)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one or two optionally substituted cycloalkyl groups. In one embodiment, the cycloalkyl group(s) is an optionally substituted C_3-C_6 cycloalkyl. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a

C_1-C_4 alkyl. In another embodiment, the alkyl is a C_1 or C_2 alkyl. In another embodiment, the alkyl is substituted with one optionally substituted cycloalkyl group. In another embodiment, the alkyl is substituted with two optionally substituted cycloalkyl groups. Non-limiting exemplary (cycloalkyl)alkyl groups include:



[0460] The term "sulfonamido" as used herein by itself or as part of another group refers to a radical of the formula $-SO_2NR^{54a}R^{54b}$, wherein R^{54a} and R^{54b} are each independently hydrogen, alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl; or R^{54a} and R^{54b} taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group. Non-limiting exemplary sulfonamido groups include $-SO_2NH_2$, $-SO_2N(H)CH_3$, and $-SO_2N(H)Ph$.

[0461] The term "alkylcarbonyl" as used herein by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted by an alkyl group. In one embodiment, the alkyl is a C_1-C_4 alkyl. A non-limiting exemplary alkylcarbonyl group is $-COCH_3$.

[0462] The term "arylcarbonyl" as used herein by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted by an optionally substituted aryl group. A non-limiting exemplary arylcarbonyl group is -COPh.

[0463] The term "alkylsulfonyl" as used herein by itself or as part of another group refers to a sulfonyl group, i.e., $-SO_2-$, substituted by an alkyl group. A non-limiting exemplary alkylsulfonyl group is $-SO_2CH_3$.

[0464] The term "arylsulfonyl" as used herein by itself or as part of another group refers to a sulfonyl group, i.e., $-SO_2-$, substituted by an optionally substituted aryl group. A non-limiting exemplary arylsulfonyl group is $-SO_2Ph$.

[0465] The term "mercaptoalkyl" as used herein by itself or as part of another group refers to an alkyl substituted by a -SH group.

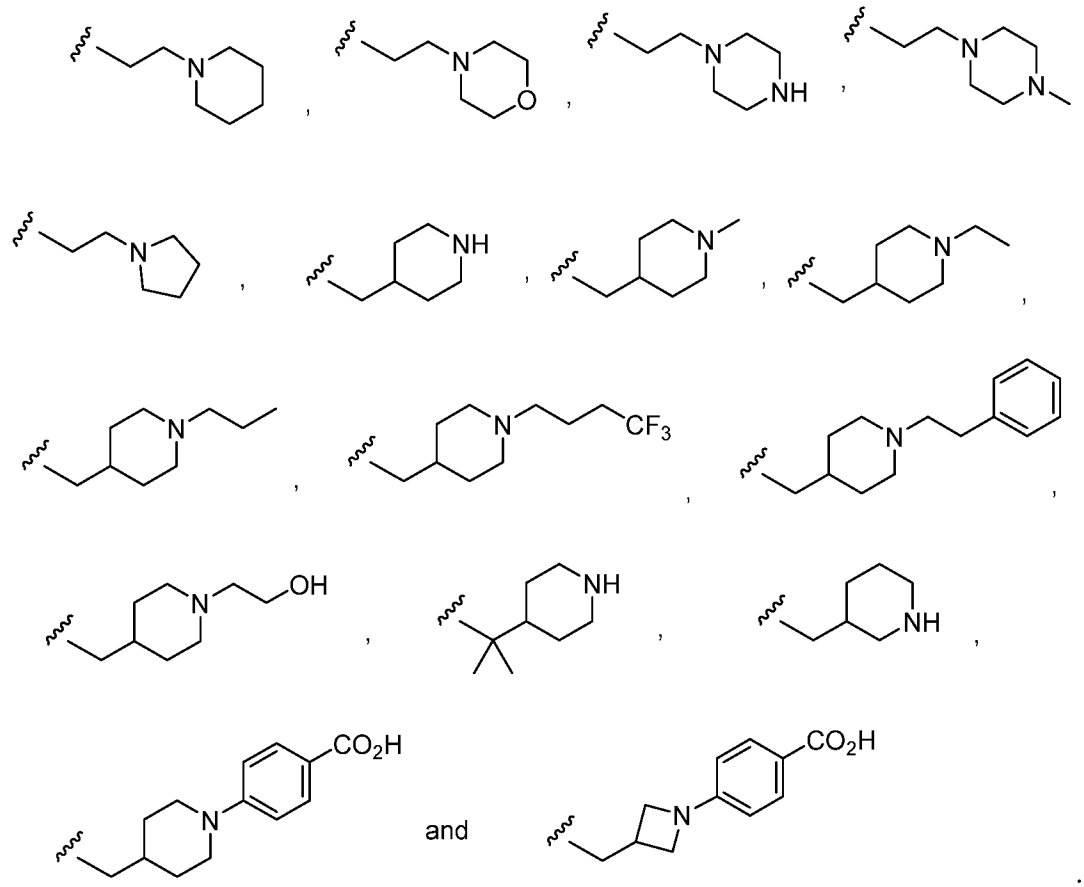
[0466] The term "carboxy" as used by itself or as part of another group refers to a radical of the formula -C(=O)OH.

[0467] The term "ureido" as used herein by itself or as part of another group refers to a radical of the formula $-NR^{51a}-C(=O)-NR^{51b}R^{51c}$, wherein R^{51a} is hydrogen or alkyl; and

R^{51b} and R^{51c} are each independently hydrogen, alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl, or R^{51b} and R^{51c} taken together with the nitrogen to which they are attached form a 4- to 8-membered optionally substituted heterocyclo group. Non-limiting exemplary ureido groups include -NH-C(C=O)-NH_2 and -NH-C(C=O)-$NHCH_3$.

[0468] The term "guanidino" as used herein by itself or as part of another group refers to a radical of the formula -NR^{52a}-C(=NR^{53})-$NR^{52b}R^{52c}$, wherein R^{52a} is hydrogen or alkyl; R^{52b} and R^{53c} are each independently hydrogen, alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl; or R^{52b} and R^{52c} taken together with the nitrogen to which they are attached form a 4- to 8-membered optionally substituted heterocyclo group; and R^{53} is hydrogen, alkyl, cyano, alkylsulfonyl, alkylcarbonyl, carboxamido, or sulfonamido. Non-limiting exemplary guanidino groups include -NH-C(C=NH)-NH_2, -NH-C(C=NCN)-NH_2, and -NH-C(C=NH)-$NHCH_3$.

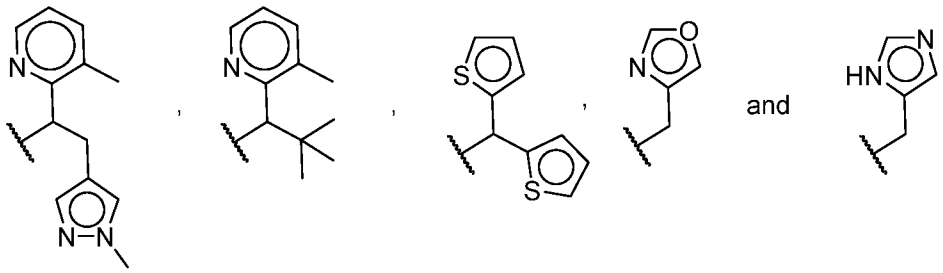
[0469] The term "(heterocyclo)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one, two, or three optionally substituted heterocyclo groups. In one embodiment, the alkyl is substituted with one optionally substituted 5- to 8-membered heterocyclo group. In another embodiment, alkyl is a C_1-C_6 alkyl. In another embodiment, alkyl is a C_1-C_4 alkyl. The heterocyclo group can be linked to the alkyl group through a carbon or nitrogen atom. Non-limiting exemplary (heterocyclo)alkyl groups include:



[0470] The term "carbamate" as used herein by itself or as part of another group refers to a radical of the formula -NR^{54a}-C(=O)-OR^{54b}, wherein R^{54a} is hydrogen or alkyl, and R^{54b} is hydrogen, alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl. A non-limiting exemplary carbamate group is -NH-(C=O)OtBu.

[0471] The term "(heteroaryl)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one or two optionally substituted heteroaryl groups. In one embodiment, the alkyl group is substituted with one optionally substituted 5- to 14-membered heteroaryl group. In another embodiment, the alkyl group is substituted with two optionally substituted 5- to 14-membered heteroaryl groups. In another embodiment, the alkyl group is substituted with one optionally substituted 5- to 9-membered heteroaryl group. In another embodiment, the alkyl group is substituted with two optionally substituted 5- to 9-membered heteroaryl groups. In another embodiment, the alkyl group is substituted with one optionally substituted 5- or 6-membered heteroaryl group. In another embodiment, the alkyl group is substituted with two optionally substituted 5- or 6-membered heteroaryl groups. In one embodiment, the alkyl group is a C_1-C_6 alkyl. In another embodiment, the alkyl group is a C_1-C_4 alkyl.

In another embodiment, the alkyl group is a C_1 or C_2 alkyl. Non-limiting exemplary (heteroaryl)alkyl groups include:



[0472] The terms "aralkyl" or "(aryl)alkyl" as used herein by themselves or as part of another group refers to an alkyl substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the alkyl is substituted with one optionally substituted aryl group. In another embodiment, the alkyl is substituted with two optionally substituted aryl groups. In one embodiment, the aryl is an optionally substituted phenyl or optionally substituted naphthyl. In another embodiment, the aryl is an optionally substituted phenyl. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl is a C_1 or C_2 alkyl. Non-limiting exemplary (aryl)alkyl groups include benzyl, phenethyl, $-CHPh_2$, and $-CH(4\text{-F-Ph})_2$.

[0473] The term "amido" as used herein by itself or as part of another group refers to a radical of formula $-C(=O)NR^{60a}R^{60b}$, wherein R^{60a} and R^{60b} are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, haloalkyl, (alkoxy)alkyl, (hydroxy)alkyl, (cyano)alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, (aryl)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, or (heteroaryl)alkyl; or R^{60a} and R^{60b} taken together with the nitrogen to which they are attached from a 4- to 8-membered optionally substituted heterocyclo group. In one embodiment, R^{60a} and R^{60b} are each independently hydrogen or C_1-C_6 alkyl.

[0474] The term "amino" as used by itself or as part of another group refers to a radical of the formula $-NR^{55a}R^{55b}$, wherein R^{55a} and R^{55b} are independently hydrogen, optionally substituted alkyl, haloalkyl, (hydroxy)alkyl, (alkoxy)alkyl, (amino)alkyl, heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, (aryl)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, or (heteroaryl)alkyl.

[0475] In one embodiment, the amino is $-NH_2$.

[0476] In another embodiment, the amino is an "alkylamino," i.e., an amino group wherein R^{55a} is C_{1-6} alkyl and R^{55b} is hydrogen. In one embodiment, R^{55a} is C_1-C_4 alkyl. Non-limiting exemplary alkylamino groups include -N(H)CH_3 and -N(H)CH_2CH_3.

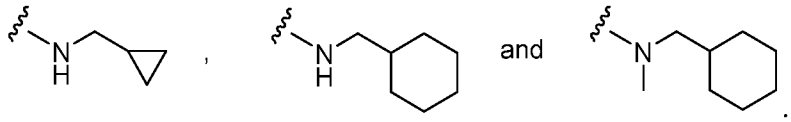
[0477] In another embodiment, the amino is a "dialkylamino," i.e., an amino group wherein R^{55a} and R^{55b} are each independently C_{1-6} alkyl. In one embodiment, R^{55a} and R^{55b} are each independently C_1-C_4 alkyl. Non-limiting exemplary dialkylamino groups include -N(CH_3)$_2$ and -N(CH_3)$CH_2CH(CH_3)_2$.

[0478] In another embodiment, the amino is a "hydroxyalkylamino," i.e., an amino group wherein R^{55a} is (hydroxyl)alkyl and R^{55b} is hydrogen or C_1-C_4 alkyl.

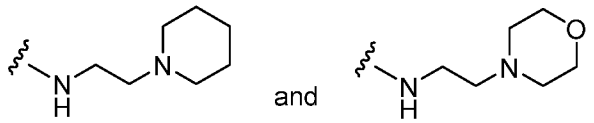
[0479] In another embodiment, the amino is a "cycloalkylamino," i.e., an amino group wherein R^{55a} is optionally substituted cycloalkyl and R^{55b} is hydrogen or C_1-C_4 alkyl.

[0480] In another embodiment, the amino is a "aralkylamino," i.e., an amino group wherein R^{55a} is aralkyl and R^{55b} is hydrogen or C_1-C_4 alkyl. Non-limiting exemplary aralkylamino groups include -N(H)CH_2Ph, -N(H)$CHPh_2$, and -N(CH_3)CH_2Ph.

[0481] In another embodiment, the amino is a "(cycloalkyl)alkylamino," i.e., an amino group wherein R^{55a} is (cycloalkyl)alkyl and R^{55b} is hydrogen or C_1-C_4 alkyl. Non-limiting exemplary (cycloalkyl)alkylamino groups include:



[0482] In another embodiment, the amino is a "(heterocyclo)alkylamino," i.e., an amino group wherein R^{55a} is (heterocyclo)alkyl and R^{55b} is hydrogen or C_1-C_4 alkyl. Non-limiting exemplary (heterocyclo)alkylamino groups include:



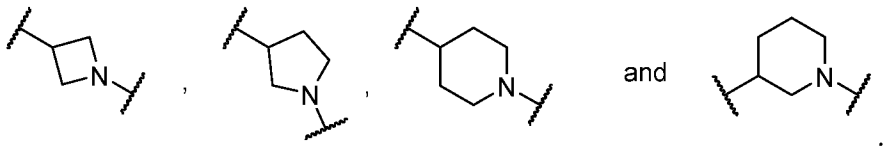
[0483] The term "(amino)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one amino group. In one embodiment, the amino group is -NH_2. In one embodiment, the amino group is an alkylamino. In another embodiment, the amino group is a dialkylamino. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. Non-limiting exemplary (amino)alkyl groups include -CH_2NH_2, $CH_2CH_2N(H)CH_3$, -$CH_2CH_2N(CH_3)_2$, CH_2N(H)cyclopropyl, -CH_2N(H)cyclobutyl, and -CH_2N(H)cyclohexyl, and -$CH_2CH_2CH_2N(H)CH_2$Ph and -$CH_2CH_2CH_2N(H)CH_2$(4-CF_3-Ph).

[0484] In the present disclosure, the term "alkylenyl" as used herein by itself or part of another group refers to a divalent form of an alkyl group, wherein the alkyl group is either unsubstituted or substituted with one or two groups independently selected from the group consisting of optionally substituted phenyl and optionally substituted 5- or 6-membered heteroaryl. In one embodiment, the alkylenyl is a divalent form of a C_{1-12} alkyl, i.e., a C_1-C_{12} alkylenyl. In one embodiment, the alkylenyl is a divalent form of a C_{1-10} alkyl, i.e., a C_1-C_{10} alkylenyl. In one embodiment, the alkylenyl is a divalent form of a C_{1-8} alkyl, i.e., a C_1-C_8 alkylenyl. In one embodiment, the alkylenyl is a divalent form of an unsubstituted C_{1-6} alkyl, i.e., a C_1-C_6 alkylenyl. In another embodiment, the alkylenyl is a divalent form of an unsubstituted C_{1-4} alkyl, i.e., a C_1-C_4 alkylenyl. In another embodiment, the alkylenyl is a divalent form of a C_{1-4} alkyl substituted with one or two optionally substituted phenyl groups. Non-limiting exemplary alkylenyl groups include -CH_2-, -CH_2CH_2-, -CH(Ph)-, -CH(Ph)CH_2-, -$CH_2CH_2CH_2$-, -CH(Ph)CH_2CH_2-, -$CH_2(CH_2)_2CH_2$-, -$CH(CH_2)_3CH_2$-, and -$CH_2(CH_2)_4CH_2$-.

[0485] The term "heteroalkylenyl" as used herein by itself or part of another group refers to a divalent form of a heteroalkyl group. In one embodiment, the heteroalkylenyl is a divalent form of a 3- to 20-membered heteroalkyl, i.e., a 3- to 20-membered heteroalkylenyl. In another embodiment, the heteroalkylenyl is a divalent form of a 3- to 10-membered heteroalkyl, i.e., a 3- to 10-membered heteroalkylenyl. In another embodiment, the heteroalkylenyl is a divalent form of a 3- to 8-membered heteroalkyl, i.e., a 3- to 8-membered heteroalkylenyl. In another embodiment, the heteroalkylenyl is a divalent form of a 3- to 6-membered heteroalkyl, i.e., a 3- to 6-membered heteroalkylenyl. In another embodiment, the heteroalkylenyl is a divalent form of a 3- or 4-membered heteroalkyl, i.e., a 3- or 4-membered heteroalkylenyl. In another embodiment, the heteroalkylenyl is a radical of the formula -$(CH_2CH_2O)_{u1}$- wherein u_1 is 1, 2, 3, 4, 5, or 6. Non-limiting exemplary heteroalkylenyl groups include -CH_2OCH_2-, -$CH_2CH_2OCH_2CH_2O$-, -$CH_2OCH_2CH_2CH_2$-, and -$CH_2CH_2OCH_2CH_2OCH_2CH_2O$-.

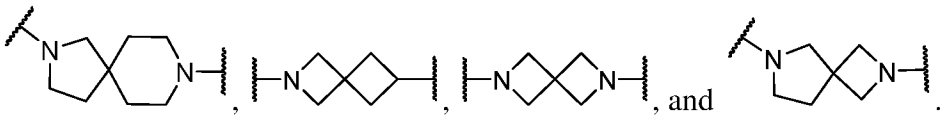
[0486] The term "heterocyclenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted heterocyclo group. In another embodiment, the heterocyclenyl is a divalent form of a 4- to 14-membered heterocyclo group, i.e., a 4- to 14-membered heterocyclenyl. In another embodiment, the heterocyclenyl is a divalent form of a 4- to 10-membered heterocyclo group, i.e., a 4- to 10-membered heterocyclenyl. In another embodiment, the heterocyclenyl is a divalent form of a 4- to 8-membered heterocyclo group, i.e., a 4- to 8-membered heterocyclenyl.

In one embodiment, the heterocyclenyl is a divalent form of an optionally substituted azetidine. In another embodiment, the heterocyclenyl is a divalent form of an optionally substituted piperidinyl. In another embodiment, the heterocyclenyl is a divalent form of an optionally substituted piperazinyl. Non-limiting exemplary heterocyclenyl groups include:

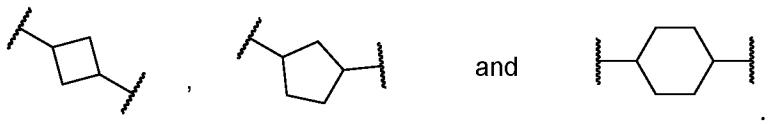


In another embodiment, the heterocyclenyl is a spiroheterocyclenyl.

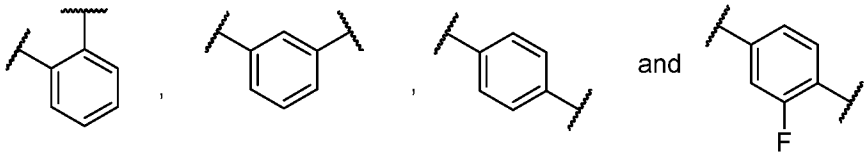
[0487] The term "spiroheterocyclenyl" as used herein by itself or part of another group refers to a divalent form of a spiroheterocyclo. Non-limiting exemplary spiroheterocyclenyl groups include:



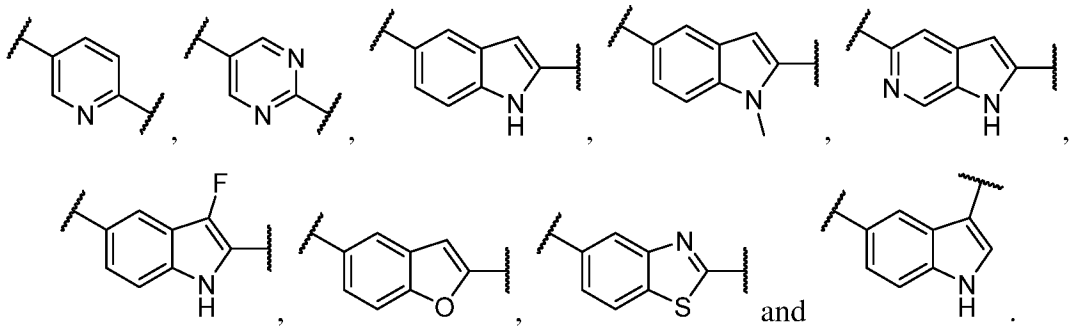
[0488] The term "cycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted C_4-C_6 cycloalkyl group. In one embodiment, the cycloalkylenyl is a 4-membered cycloalkylenyl. In another embodiment, the cycloalkylenyl is a 5-membered cycloalkylenyl. In another embodiment, the cycloalkylenyl is a 6-membered cycloalkylenyl. Non-limiting exemplary groups include:



[0489] The term "phenylenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted phenyl group. Non-limiting examples include:



[0490] The term "heteroarylenyl" as used herein by itself or part of another group refers to a divalent form of an optionally substituted heteroaryl group, e.g., a 5- to 9-membered heteroarylenyl. In one embodiment, the heteroarylenyl is a 6-membered heteroarylenyl, e.g., heteroarylenyl derived from pyridine. In one embodiment, the heteroarylenyl is a bicyclic 9-membered heteroarylenyl. Exemplary non-limiting exemplary heteroarylenyl groups include:



[0491] The present disclosure encompasses any of the Compounds of the Disclosure being isotopically-labelled (i.e., radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H (or deuterium (D)), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively, e.g., ^{3}H, ^{11}C, and ^{14}C. In one embodiment, provided is a composition wherein substantially all of the atoms at a position within the Compound of the Disclosure are replaced by an atom having a different atomic mass or mass number. In another embodiment, provided is a composition wherein a portion of the atoms at a position within the Compound of the disclosure are replaced, i.e., the Compound of the Disclosure is enriched at a position with an atom having a different atomic mass or mass number. For example, in some particular embodiments, the hydrogen atom at R^3 in any one of Formulae **I-IV** can be replaced with a deuterium atom.

[0492] When a position of any one of Formulae **I-IV**, e.g., R^3, is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural abundance isotopic composition.

[0493] When a position of any one of Formulae **I-IV**, e.g., R^3, is designated specifically as "D" or "deuterium," the position is understood to have deuterium at an abundance that is at least about 1000 times greater than the natural abundance of deuterium, which is about 0.015%.

[0494] Isotopically-labelled Compounds of the Disclosure can be prepared by methods known in the art.

[0495] Compounds of the Disclosure may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure encompasses the use of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers can be separated according to methods known in the art in view of the present disclosure. When

the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are also encompassed by the present disclosure.

[0496] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0497] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[0498] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

[0499] The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive. In one embodiment, Compounds of the Disclosure are racemic.

[0500] The term "absolute configuration" refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, e.g., R or S.

[0501] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure & Appl. Chem 68*:2193 (1996), unless otherwise indicated.

[0502] The term "enantiomeric excess" or "ee" refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of *R* and *S* enantiomers, the percent enantiomeric excess is defined as $|R - S| * 100$, where *R* and *S* are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([\alpha]_{obs}/[\alpha]_{max}) * 100$, where $[\alpha]_{obs}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{max}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography or optical polarimetry.

[0503] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

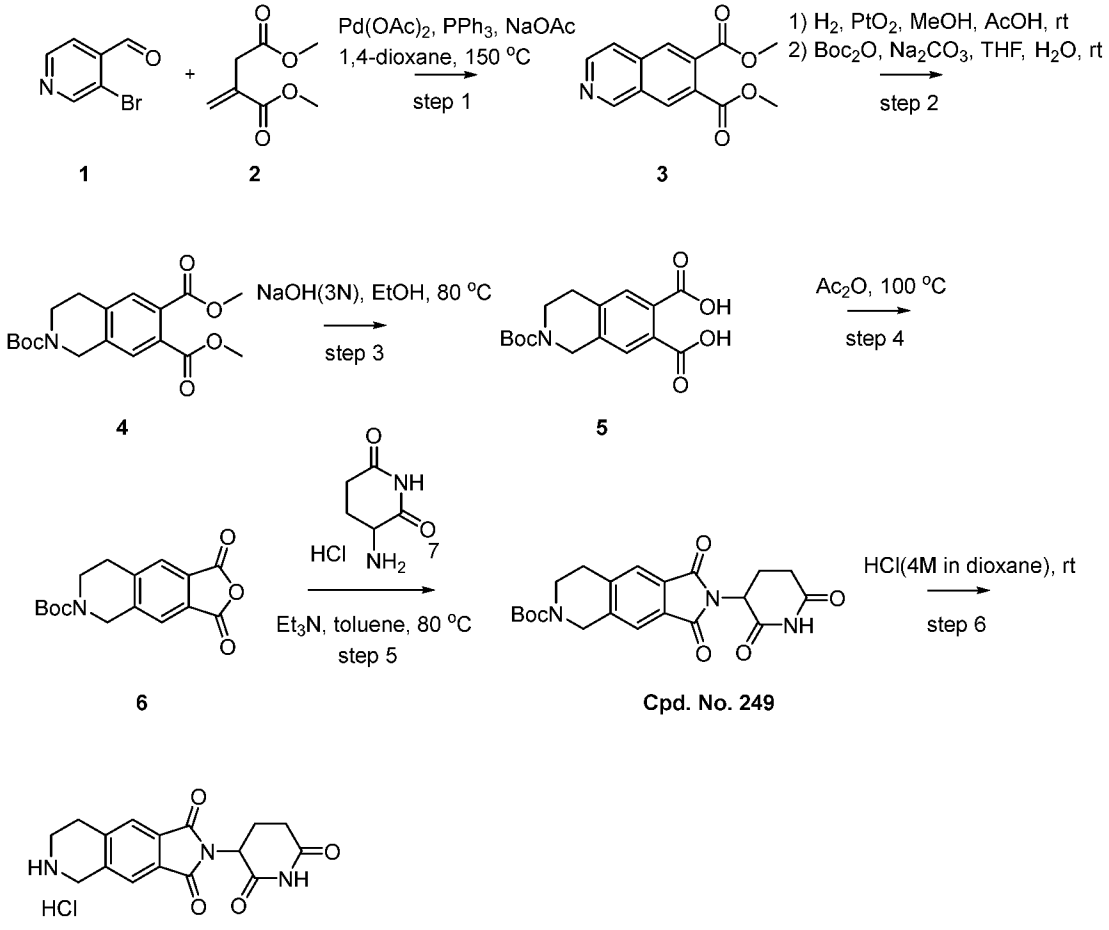
EXAMPLES

EXAMPLE 1

Synthesis of tert-butyl 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,5,7,8-hexahydro-6H-pyrrolo[3,4-g]isoquinoline-6-carboxylate (Cpd. No. 249)

and

2-(2,6-dioxopiperidin-3-yl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione (Cpd. No. 241)



1 2 3 4 5 6 Cpd. No. 249

Cpd. No. 241

[0504] Step 1: Synthesis of dimethyl isoquinoline-6,7-dicarboxylate (compound **3**)

[0505] A mixture of 3-bromopyridine-4-carbaldehyde (**1**, 0.093 g, 0.5 mmol), dimethyl itaconate (**2**, 0.079 g, 0.5 mmol), $Pd(OAc)_2$ (0.0056 g, 0.025 mmol), PPh3 (0.013 g, 0.05 mmol) and NaOAc (0.123 g, 1.5 mmol) in dioxane (10mL) was placed in a 50 mL pressure vessel. After the system was flushed with argon, the reaction mixture was allowed to react at 150 °C for 24 h, and then the reaction mixture was cooled to room temperature. The reaction mixture was filtered through celite® to eliminate inorganic salts and washed by ethyl acetate. Removal of the solvent left a crude mixture which was

purified by flash chromatography on silica gel (ethyl acetate–hexane) to give dimethyl isoquinoline-6,7-dicarboxylate (**3**, 0.082 g, 67%).

[0506] Step 2: Synthesis of 2-(*tert*-butyl) 6,7-dimethyl 3,4-dihydroisoquinoline-2,6,7(1*H*)-tricarboxylate (compound **4**)

[0507] Compound **3** (279.6 mg, 1.14 mmol) was dissolved in mixture solvent of methanol (4 mL) and acetic acid (0.2 mL). PtO_2 (30 mg) was added, and the reaction mixture was stirred under hydrogen at room temperature for 4h. The reaction mixture was filtered through celite®. The filtrate was collected and concentrated under reduced pressure to give the crude product.

[0508] The crude product was dissolved in mixture of THF (4 mL) and water (1 mL), and Na_2CO_3 (500 mg) and Boc_2O (500 mg, 2.28 mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to remove the THF, and the crude mixture dissolved in water (5 mL) and ethyl acetate (10 mL). The organic layer was separated, washed with water and brine, dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash chromatography on silica gel (ethyl acetate–hexane) to give compound **4** (130 mg).

[0509] Step 3: Synthesis of 2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylic acid (compound **5**)

[0510] 3N NaOH (0.37 mL, 1.12 mmol) was added to a solution of compound **4** (130 mg, 0.37 mmol) in EtOH (3.7 mL) and the resulting mixture heated at 80°C for 2 h. The reaction was concentrated under reduced pressure and the crude mixture dissolved in water (5 mL) and ethyl acetate (10 mL) and then acidified using 1N HCl to pH ~4 in an ice bath. The organic layer was separated and the aqueous layer was extracted with ethyl acetate two more times. The combined the organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was used in the next step without further purification.

[0511] Step 4: Synthesis of *tert*-butyl 1,3-dioxo-1,5,7,8-tetrahydrofuro[3,4-*g*]isoquinoline-6(3*H*)-carboxylate (compound **6**)

[0512] Compound **5** (the crude product from step 3) was dissolved in acetic anyhydride (2 mL) and the reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was cooled to room temperature, and 10 mL ethyl acetate was added. The reaction mixture waas washed with water and brine, dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash chromatography on silica gel (ethyl acetate–hexane) to give compound **6** (123.1 mg).

[0513] Step 5: Synthesis of *tert*-butyl 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,5,7,8-hexahydro-6H-pyrrolo[3,4-*g*]isoquinoline-6-carboxylate (Cpd. No. 249)

[0514] Compound **6** (123.1 mg, 0.41 mmol), compound **7** (73.5 mg, 0.45 mmol) and Et_3N (0.17 mL, 1.23 mmol) were added to toluene (5 mL). The reaction mixture was stirred at 80 °C for 3 h and then cooled to room temperature. The reaction was concentrated under reduced pressure and the crude mixture dissolved in water (5 mL) and ethyl acetate (10 mL). The organic layer was separated, washed with water and brine, dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash chromatography (ethyl acetate–hexane) to give Cpd. No. 249.

[0515] Step 6: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,4-*g*]isoquinoline-1,3(2*H*)-dione (Cpd. No. 241).

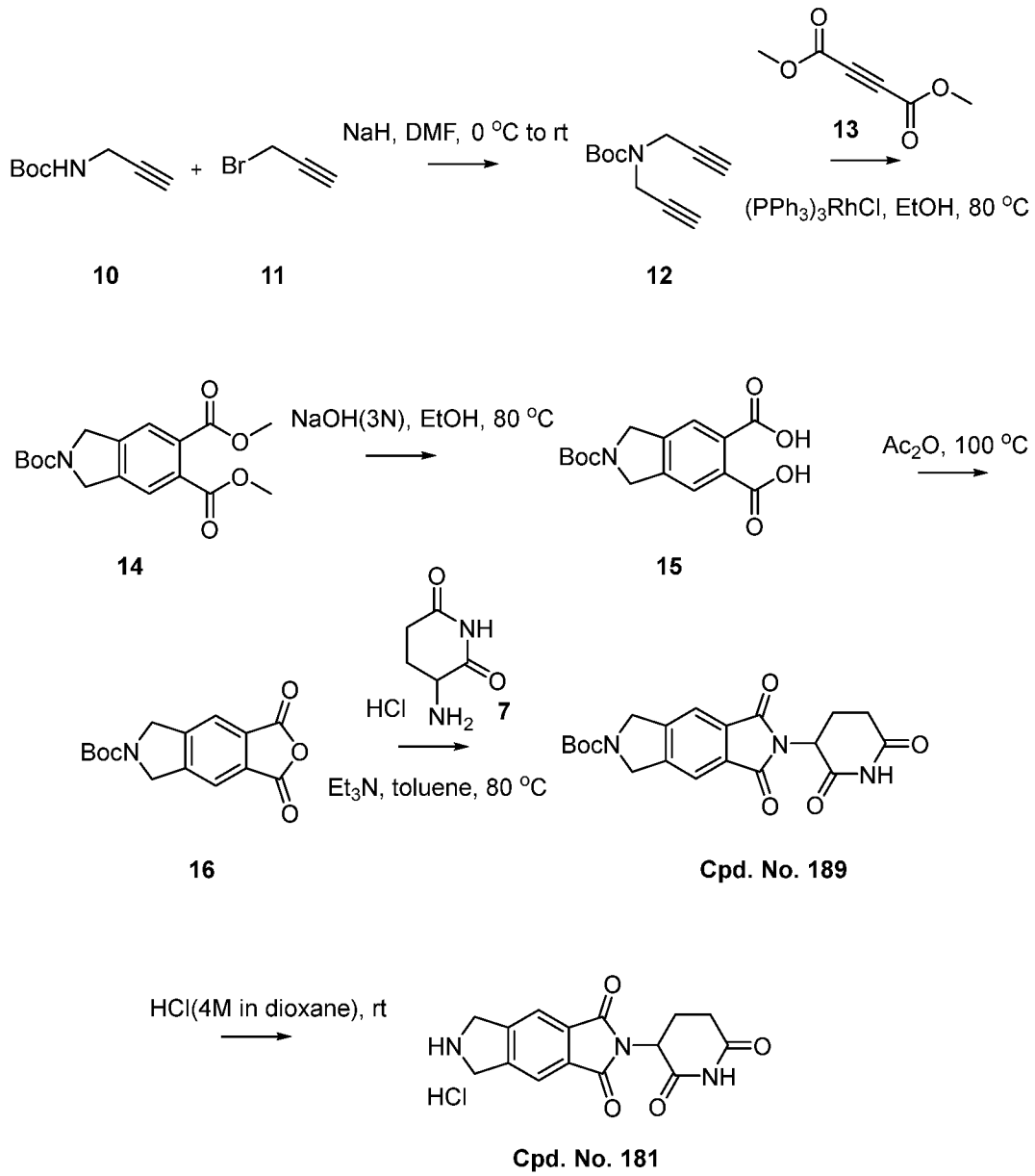
[0516] Cpd. No. 249 (102.1 mg, 0.24 mmol) was added to 1 mL HCl (4M in 1,4-dioxane), and the mixture reaction mixture was stirred at room temperature for 2 h. The 1,4-dioxane was removed under reduced pressure to give Cpd. No. 241 as the HCl salt.

EXAMPLE 2

Synthesis of tert-butyl 6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindole-2(1H)-carboxylate (Cpd. No. 189)

and

2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione (Cpd. No. 181)



[0517] Step 1: Synthesis of *tert*-butyl di(prop-2-yn-1-yl)carbamate (compound **12**)

[0518] A solution of N-(tert-butyloxy)carbonyl propargylamine (compound **10**; 33.36 g, 215 mmol) in 50 mL of DMF was treated portionwise (4 times) with 60% NaH (10.4 g) at 0 °C. After stirring for 30 min at 25 °C, 39 mL of an 80% solution of propargyl bromide (compound **11**) in toluene was added. The reaction mixture was stirred for an additional 5 h at 25°C, and then quenched with the addition of ice-water. The mixture was extracted with Et_2O (3 × 200mL), and the combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography on silica gel (ethyl acetate–hexane) to give compound **12.**

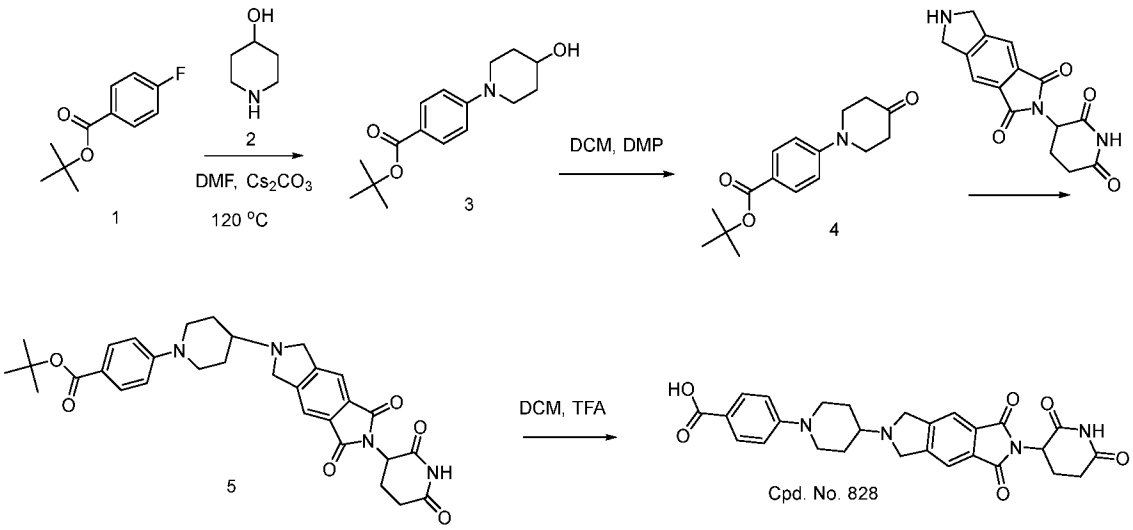
[0519] Step 2: Synthesis of 2-(*tert*-butyl) 5,6-dimethyl isoindoline-2,5,6-tricarboxylate (compound **14**)

[0520] A solution of compound **12** (10.4 g, 53.9 mmol) and dimethyl acetylenedicarboxylate (compound **13**, 30.7 g, 216 mmol) in 110 mL of absolute EtOH was degassed by bubbling N_2 through the solution for 10 min. To this solution was added 1.0 g (0.02 equiv) of Wilkinson's catalyst ($(Ph_3P)_3RhCl$) at 25 °C. After being warmed at reflux for 18 h, the reaction mixture was cooled to 25 °C and concentrated in vacuo. The resulting brown residue was diluted in 200 mL of Et_2O, and the precipitate was removed by filtration over Celite®. The filtrate was concentrated and the crude product purified by column chromatography on silica gel (20% EtOAc/hexane) to give 4.60 g (26%) of compound **14.**

[0521] The remaining steps for synthesizing Cpd. No. 181 (as the HCl salt) are essentially the same as Steps 3 -6 described above in EXAMPLE 1.

EXAMPLE 3

Synthesis of 4-(4-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidin-1-yl)benzoic acid (Cpd. No. 828)



[0522] Compound 1 (1.0 eq) and compound 2 (1.5 eq) were dissolved in DMF, and Cs_2CO_3 (4 eq) was added. The reaction mixture was stirred overnight at 120 °C. The reaction was partitioned between EtOAc and H_2O, and the organic layer was washed with brine. The concentrated crude product was purified on a Combiflash chromatography system using EtOAc/hexane as the eluent to give compound 3 in about 60% yield. Compound 3 demonstrated high UV absorption at 280 nm, but low absorption at 254 nm.

[0523] Compound 3 (1.0 eq) was dissolved in DCM, and Dess-Martin reagent (1.3 eq) was added. The reaction mixture was stirred at rt for 4 h. The reaction was partitioned between EtOAc and H_2O, and the organic layer was washed with brine. The concentrated

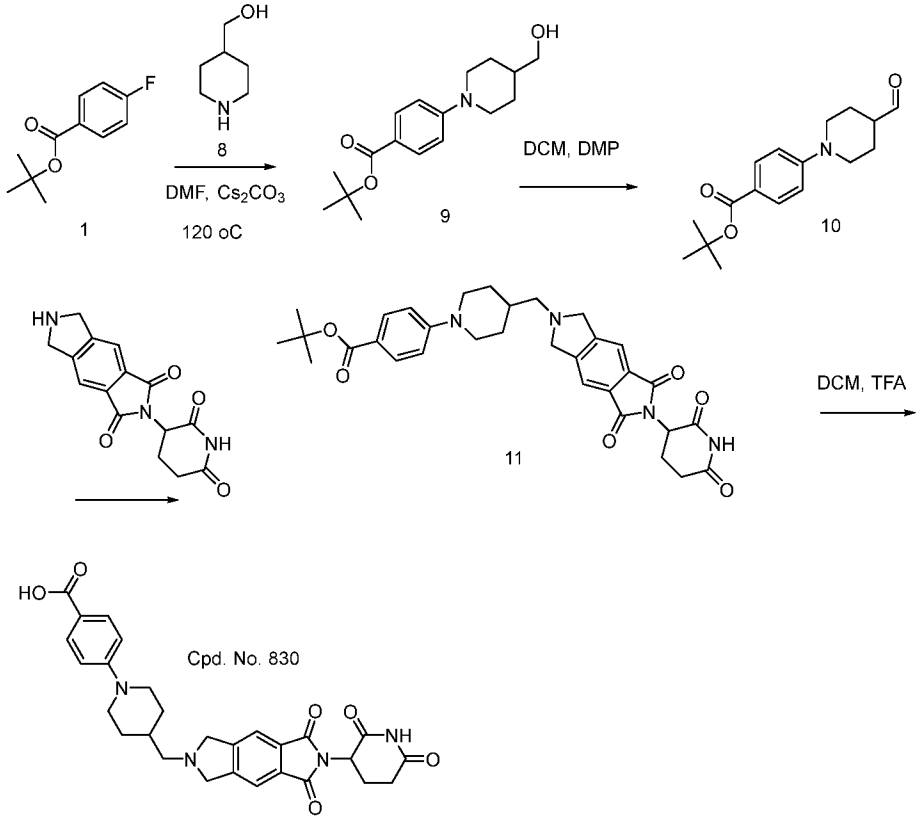
crude product was purified on a Combiflash chromatography system using EtOAc/hexane as the eluent to give compound 4 in about 85% yield.

[0524] Cpd. No 181 (see Example 2) and TEA (1.5 eq) were dissolved in DCE. Compound 4 and AcOH (4 eq) were added. The mixture was stirred overnight. $NaB(OAc)_3H$ (3 eq) was added and the reaction was complete in about 3 h. The reaction mixture was concentrated with silica gel and purified on a Combiflash chromatography

[0525] Compound 5 was dissolved in DCM and TFA (20X) was added. THe solvent and TFA were removed to give Cpd. No. 828.

EXAMPLE 4

Synthesis of 4-(4-((6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)methyl)piperidin-1-yl)benzoic acid (Cpd. No. 830)



[0526] Compound 1 (1.0 eq) and compound 8 (1.5 eq) were dissolved in DMF, and Cs_2CO_3 (4 eq) was added. The reaction mixture was stirred overnight at 120 °C. The reaction was partitioned between EtOAc and H_2O, and the organic layer was washed with brine. The concentrated crude product was purified on a Combiflash chromatography system using EtOAc/hexane as the eluent to give compound 9 in about 60% yield. Compound 9 demonstrated high UV absorption at 280 nm, but low absorption at 254 nm.

[0527] Compound 9 (1.0 eq) was dissolved in DCM, and Dess-Martin reagent (1.3 eq) was added. The reaction mixture was stirred at rt for 4 h. The reaction was partitioned

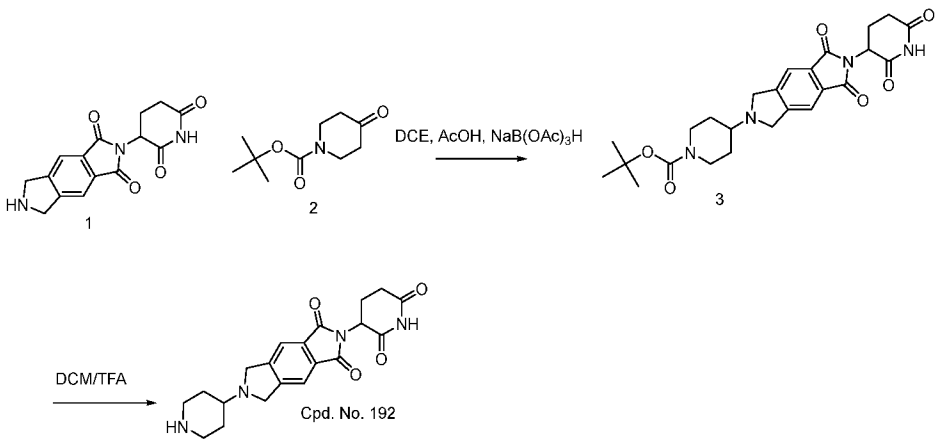
between EtOAc and H_2O, and the organic layer was washed with brine. The concentrated crude product was purified on a Combiflash chromatography system using EtOAc/hexane as the eluent to give compound 10 in about 85% yield.

[0528] Compound 18 (see Example 21) and TEA (1.5 eq) were dissolved in DCE. Compound 10 and AcOH (4 eq) were added. The mixture was stirred overnight. $NaB(OAc)_3H$ (3 eq) was added and the reaction was complete in about 3 h. The reaction mixture was concentrated with silica gel and purified on a Combiflash chromatography system using DCM/MeOH (5%) as the eluent to give compound 11.

[0529] Compound 11 was dissolved in DCM and TFA (20X) was added. The solvent and TFA were removed to give Cpd. No. 830.

EXAMPLE 5

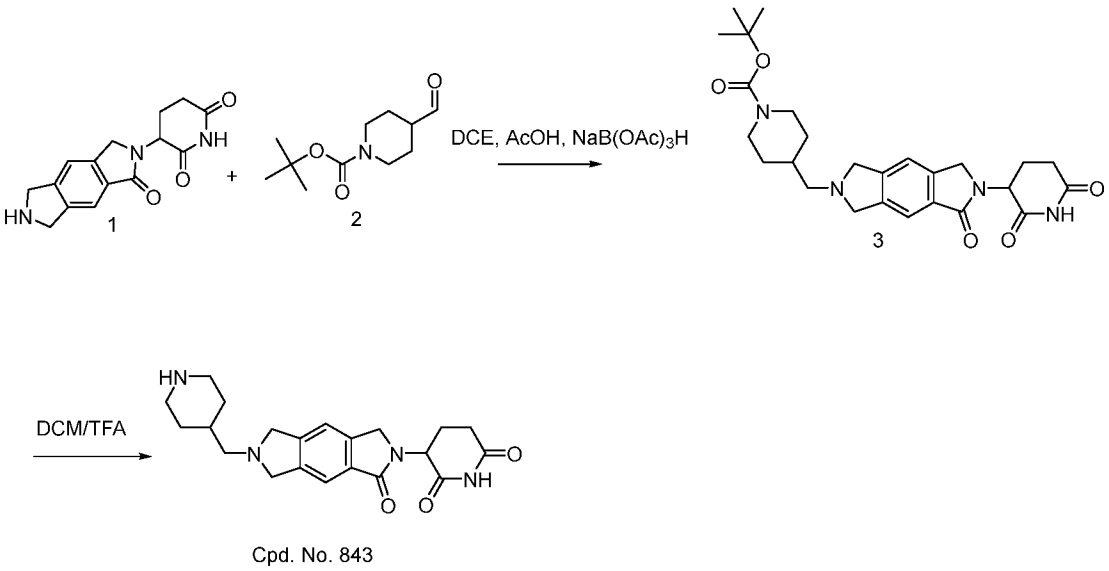
Synthesis of 2-(2,6-dioxopiperidin-3-yl)-6-(piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione (Cpd. No. 192)



[0530] Compound 1 (1.0 eq) was dissolved in DCE (10 X), and compound 2 (2.0 eq) and AcOH (3 eq.) were added. The mixture was stirred at rt for 2 h. Molecular sieves (4 angstrom) (3X) were added, and the mixture was stirred for 12 h. $NaB(OAc)_3H$ (3.0 eq) was added, and the mixture was stirred at rt overnight. The reaction was concentrated and purified on a Combiflash chromatography system using MeOH/DCM as the eluent to provide compound 3 in 70% yield. Compound 3 was dissolved in 10X DCM, and TFA (2X) was added. The reaction mixture was stirred at rt for 2 h. The solvent was distilled and dried on the lyophilizer overnight to give Cpd. No. 192.

EXAMPLE 6

Synthesis of 3-(1-oxo-6-(piperidin-4-ylmethyl)-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione (Cpd. No. 843)

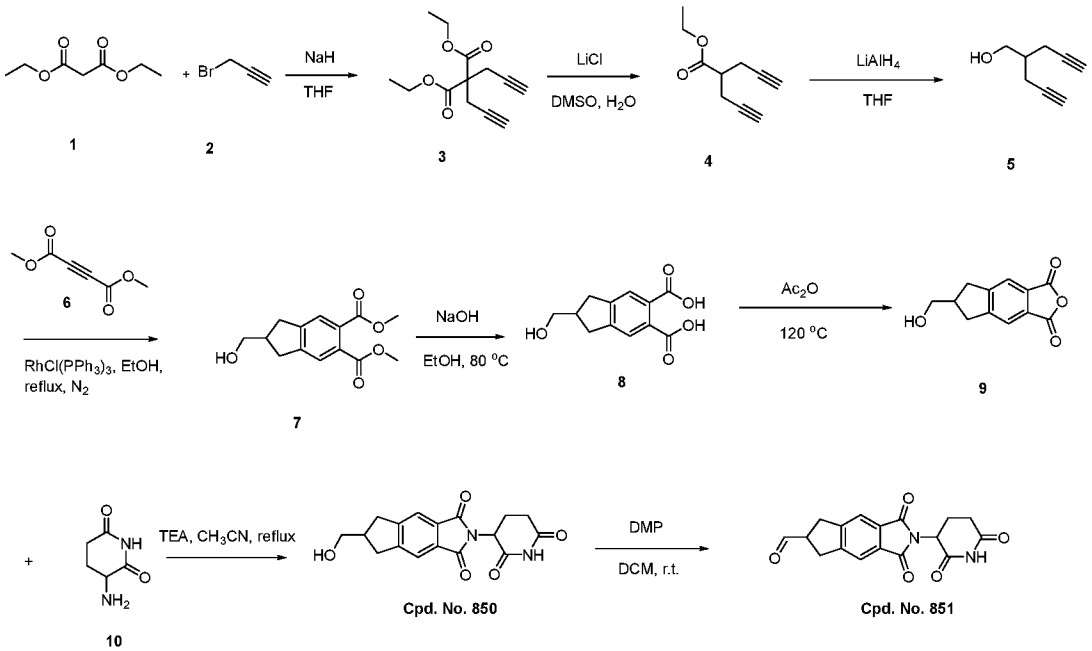


Cpd. No. 843

[0531] Compound 1 (1.0 eq) was dissolved in DCE (10 X), and compound 2 (2.0 eq) and AcOH (3 eq.) were added. The mixture was stirred at rt for 2 h. Molecular sieves (4 angstrom) (3X) were added, and the mixture was stirred for 12 h. $NaB(OAc)_3H$ (3.0 eq) was added, and the mixture was stirred at rt overnight. The reaction was concentrated and purified on a Combiflash chromatography system using MeOH/DCM as the eluent to give compound 3 in 90% yield. Compound 3 was dissolved in 10X DCM, and TFA (2X) was added. The reaction mixture was stirred at rt for 2 h. The solvent was removed and the product was dried on the lyophilizer overnight to give Cpd. No. 843.

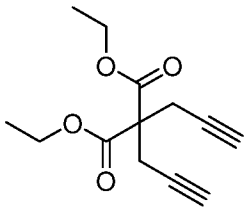
EXAMPLE 7

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,5,6,7-exahydrocyclopenta[f]isoindole-6-carbaldehyde (Cpd. No. 851)



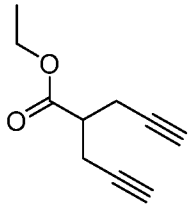
Cpd. No. 850 Cpd. No. 851

[0532] Step 1: Synthesis of diethyl 2,2-di(prop-2-yn-1-yl)malonate.



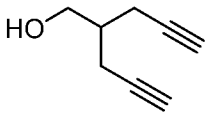
[0533] To a suspension of sodium hydride (60% wt in mineral oil, 4.22 g, 105.5 mmol) in dry THF (100 mL) stirring at –10 °C, dimethyl malonate (6.0 mL, 52.5 mmol) was added dropwise over 10 min. The reaction mixture was stirred at –10 °C for 5 min, and then propargyl bromide (80% wt. in toluene, 12.0 mL, 107.7 mmol) was added dropwise. The reaction mixture was warmed to 25 °C and stirred for 20 h. The reaction mixture was then poured into H_2O (50 mL) and Et_2O (50 mL), and the layers were separated. The aq layer was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator leaving a white solid. The solid was recrystallized from ethyl acetate and hexanes resulting in 9.44 g of a crystalline white solid (84% yield).

[0534] Step 2: Synthesis of ethyl 2-(prop-2-yn-1-yl)pent-4-ynoate.



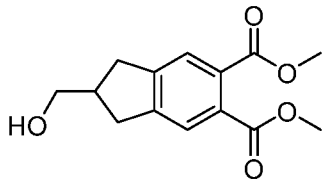
[0535] Dimethyl 2,2-di(2-propynyl)malonate (4.70 g, 22.6 mmol) and lithium chloride (2.95 g, 69.7 mmol) were dissolved in a solution of H_2O (1.0 mL, 55.5 mmol) and DMSO (40 mL). This solution was then heated to reflux for 1 h. After cooling, the reaction mixture was poured into $CHCl_3$ (40 mL) and H_2O (40 mL). The layers were separated and the aq layer was extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried, filtered through silica gel, and concentrated, leaving a yellow oil. The crude oil was purified by flash chromatography on a silica gel column using 20% EtOAc in hexanes as the eluent resulting in 3.06 g of a pale yellow oil (90% yield).

[0536] Step 3: Synthesis of ethyl 2-(prop-2-yn-1-yl)pent-4-yn-1-ol.



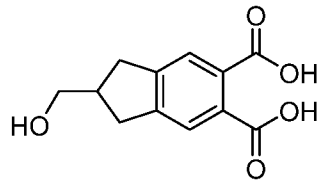
[0537] To a suspension of lithium aluminum hydride (1.25 g, 33.0 mmol) in dry THF (40 mL) stirring at -10 °C was added a solution of methyl 2-(2-propynyl)-4-pentynoate (3.06 g, 20.4 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. The reaction mixture was then quenched through the dropwise addition of H_2O (1.25 mL), an aq 10% NaOH solution (1.25 mL), and then additional H_2O (3.75 mL). The reaction mixture was then stirred for 30 min until the suspended solids turned white. The mixture was then filtered, and the solids were washed with diethyl ether (100 mL). The resulting solution was concentrated on a rotary evaporator yielding a pale yellow oil. The crude oil was purified by flash chromatography on a silica gel column using 10% EtOAc in hexanes as the eluent, resulting in 1.95 g of a clear oil (78% yield).

[0538] Step 4: Synthesis of dimethyl 2-(hydroxymethyl)-2,3-dihydro-1H-indene-5,6-dicarboxylate.



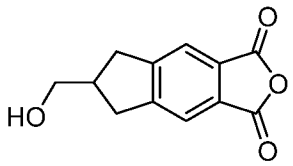
[0539] A solution of **5** and dimethyl acetylenedicarboxylate (**6**, 30.7 g, 216 mmol) in 110 mL of absolute EtOH was degassed by bubbling N_2 through the solution for 10 min. To this was added 1.0 g (0.02 equiv) of Wilkinson's catalyst ($(Ph_3P)_3RhCl$) at 25 °C. After being warmed at reflux for 18 h, the reaction mixture was cooled to 25 °C and then concentrated in vacuo. The resulting brown residue was diluted in 200 mL of Et_2O, and the precipitate was removed by filtration over Celite®. The filtrate was concentrated and the crude product purified by column chromatography (20% EtOAc/hexane) to give 4.60g (26%) of compound **7.**

[0540] Step 5: Synthesis of 2-(hydroxymethyl)-2,3-dihydro-1H-indene-5,6-dicarboxylic acid.



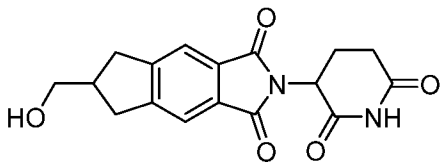
[0541] NaOH (3N) was added to a solution of **7** in EtOH and stirred at 80 °C for 4 h. Then the EtOH was removed under reduced pressure, the pH was adjusted to acidity with 2M HCl and the mixture was extracted with EtOAc. The solvent was removed to afford the product **8** which was used without further purification.

[0542] Step 6: Synthesis of 6-(hydroxymethyl)-6,7-dihydro-1H-indeno[5,6-c]furan-1,3(5H)-dione



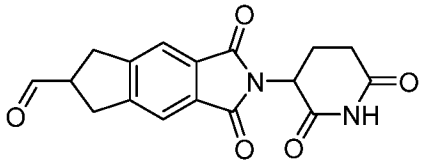
[0543] The mixture of **8** in Ac_2O was stirred at 120 °C for 6 hours. All volatiles were removed and the residue was chromatographed on silica gel to afford **9**.

[0544] Step 7: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-6-(hydroxymethyl)-6,7-dihydrocyclopenta[f]isoindole-1,3(2H,5H)-dione (Cpd. No. 850).



[0545] To a solution of **9** and **10** in toluene was added TEA (3 eq.). The mixture was stirred at reflux for 8 hours. All volatiles were removed and the residue was chromatographed on silica gel to afford Cpd. No. 850.

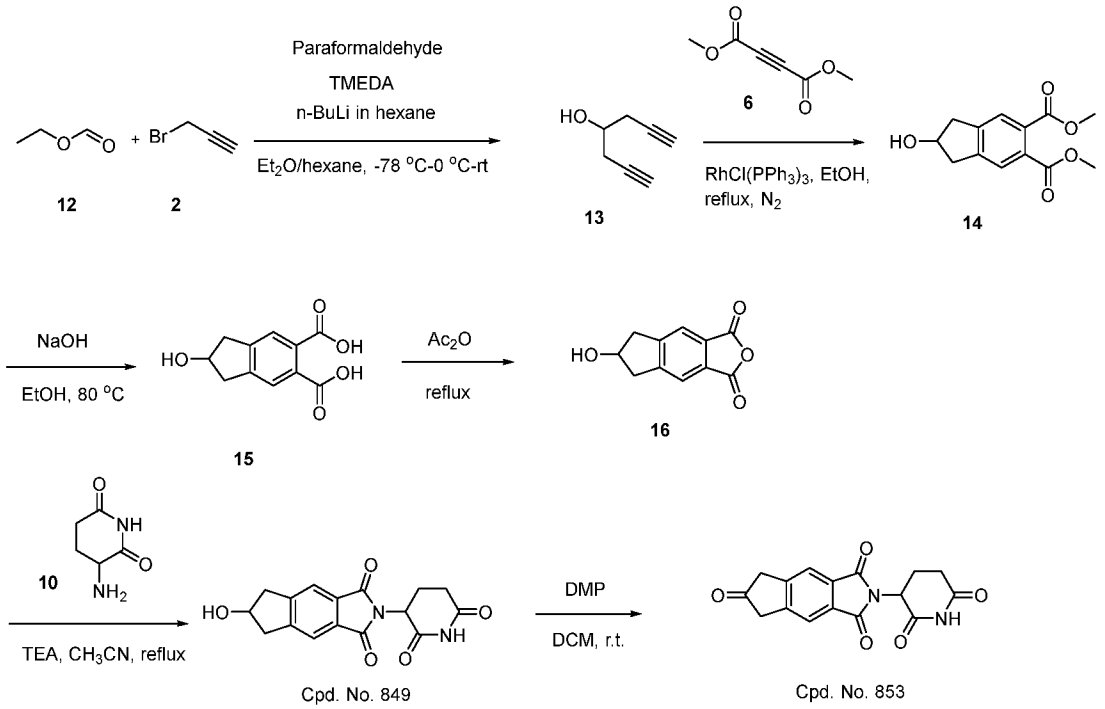
[0546] Step 8: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,5,6,7-hexahydrocyclopenta[f]isoindole-6-carbaldehyde (Cpd. No. 851).



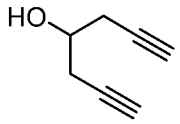
[0547] To a solution of Cpd. No. 850 in DCM was added DMP (1.2 eq.). The reaction mixture was stirred at reflux for 4 hours. All volatiles were removed and the residue was chromatographed on silica gel to afford 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,5,6,7-hexahydrocyclopenta[f]isoindole-6-carbaldehyde (Cpd. No. 851). ESI-MS: 326.09.

EXAMPLE 8

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5,7-dihydrocyclopenta[f]isoindole-1,3,6(2H)-trione (Cpd. No. 853)

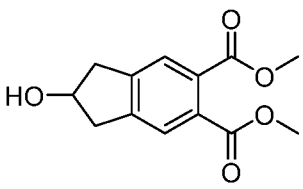


[0548] Step 1: Synthesis of hepta-1,6-diyn-4-ol.



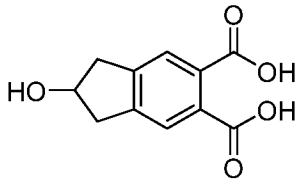
[0549] To a solution of *n*-BuLi in hexane (6.2 eq., 75 mL) in Et_2O/hexane (100 mL) was added TMEDA (7.5 mL) and **2** (3.1 eq.) by dropwise at –78 °C. The reaction mixture was stirred at –78 °C for 40 min, and then **12** in THF (20 mL) was added dropwise with 10 min. The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was then cooled to –78 °C and added 20 mL THF and Paraformaldehyde (13.5 g) in one portion. Then, the mixture was stirred at r.t. overnight. The mixture was added ice-cold NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO4, filtered, and concentrated on a rotary evaporator leaving a white solid. The solid was recrystallized from ethyl acetate and hexanes resulting in **13**.

[0550] Step 2: Synthesis of dimethyl 2-hydroxy-2,3-dihydro-1H-indene-5,6-dicarboxylate.



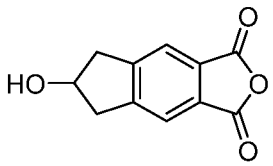
[0551] A solution of **13** and dimethyl acetylenedicarboxylate (**6**, 30.7 g, 216 mmol) in 110 mL of absolute EtOH was degassed by bubbling N_2 through the solution for 10 min. To this was added 1.0 g (0.02 equiv) of Wilkinson's catalyst ($(Ph_3P)_3RhCl$) at 25 °C. After being warmed at reflux for 18 h, the reaction mixture was cooled to 25 °C and then concentrated in vacuo. The resulting brown residue was diluted in 200 mL of Et_2O, and the precipitate was removed by filtration over Celite®. The filtrate was concentrated and the crude product purified by column chromatography (20% EtOAc/hexane) to give 4.60g (26%) of compound **14.**

[0552] Step 3: Synthesis of 2-hydroxy-2,3-dihydro-1H-indene-5,6-dicarboxylic acid.



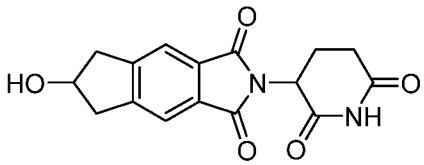
[0553] NaOH (3N) was added to a solution of **14** in EtOH and stirred at 80 °C for 4 h. Then the EtOH was removed under reduced pressure, the pH was adjusted to acidity with 2M HCl and the mixture was extracted with EtOAc. The solvent was removed to afford the product **15** which was used without further purification.

[0554] Step 4: Synthesis of 6-hydroxy-6,7-dihydro-1H-indeno[5,6-c]furan-1,3(5H)-dione.



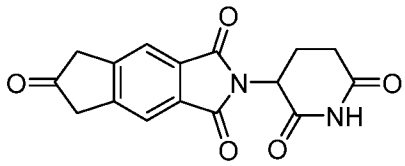
[0555] The mixture of **15** in Ac_2O was stirred at 120 °C for 6 hours. All volatiles were removed and the residue was chromatographed on silica gel to afford **16**.

[0556] Step 5: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-6-hydroxy-6,7-dihydrocyclopenta[f]isoindole-1,3(2H,5H)-dione (Cpd. No. 849).



[0557] To a solution of **16** and **10** in toluene was added TEA (3 eq.). The mixture was stirred at reflux for 8 hours. All volatiles were removed and the residue was chromatographed on silica gel to afford Cpd. No. 849.

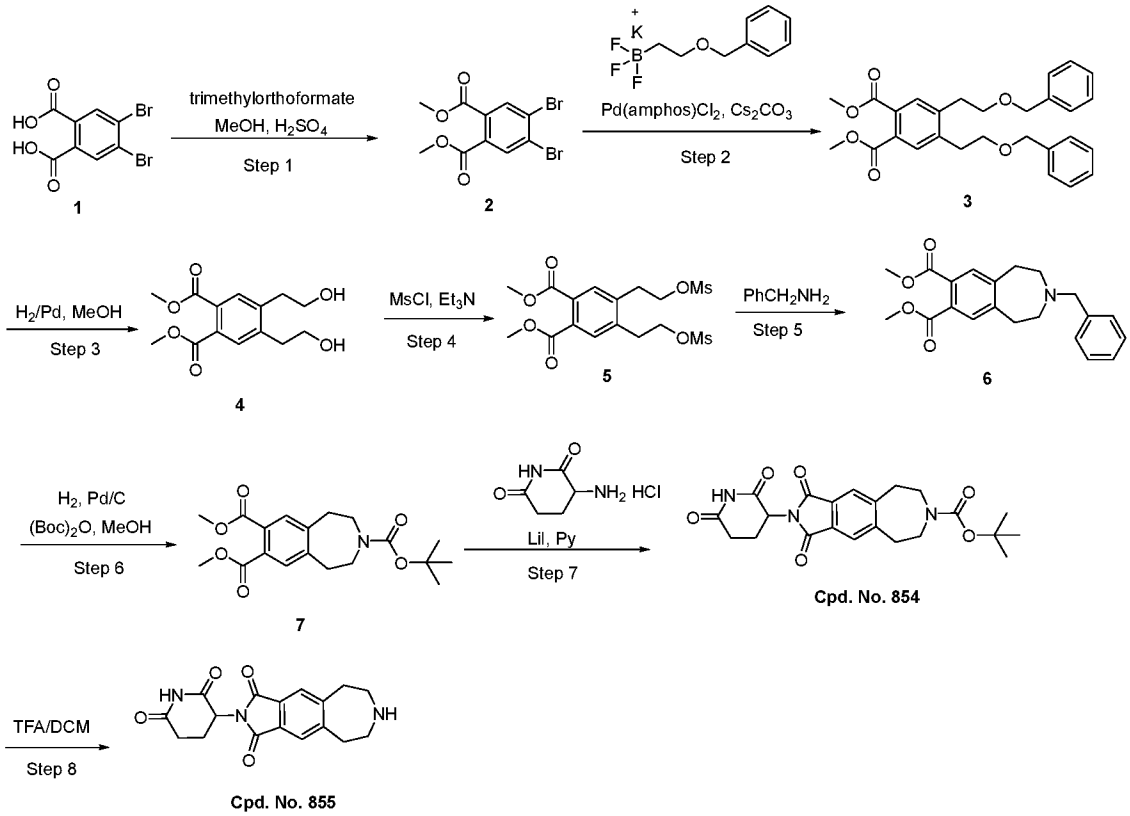
[0558] Step 6: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5,7-dihydrocyclopenta[f]isoindole-1,3,6(2H)-trione.



[0559] To a solution of Cpd. No. 849 in DCM was added DMP (1.2 eq.). The reaction mixture was stirred at reflux for 4 hours. All volatiles were removed and the residue was chromatographed on silica gel to afford intermediate 2-(2,6-dioxopiperidin-3-yl)-5,7-dihydrocyclopenta[f]isoindole-1,3,6(2H)-trione (Cpd. No. 853). ESI-MS: 312.07.

EXAMPLE 9

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione (Cpd. No. 855)



[0560] Step 1: Synthesis of Dimethyl 4,5-dibromophthalate (Compound 2)

[0561] To a solution of 4,5-dibromophthalic acid (5 g) in MeOH (25 mL) and trimethyl orthoformate (25 mL) was added conc. H_2SO_4 (2.20 mL) at room temperature, and the reaction was refluxed overnight (about 12 h), solvent was removed under vacuum, EtOAc (100 mL) and sat. aq. $NaHCO_3$ (100 mL) was added. The products were extracted with EtOAc (50 mL x 3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (m, 6H), 7.97 (s, 2H).

[0562] Step 2: Synthesis of dimethyl 4,5-bis(2-(benzyloxy)ethyl)phthalate (Compound 3)

[0563] Dimethyl 4,5-dibromophthalate (1.1 g, 3.13 mmol, 1.0 equiv), potassium (2-(benzyloxy) ethyl)trifluoroborate (1.66 g, 6.88 mmol, 2.2 equiv) and Cs_2CO_3 (4.58 g, 14.1 mmol, 4.5 equiv) was dissolved in toluene (25 mL) / water (12.5 mL). Pd(amphos)Cl_2 (325 mg, 0.46 mmol, 0.15 equiv) was added and the reaction mixture was stirred overnight (12 h) at 100 °C under N_2. After cooling to room temperature, the reaction mixture was extracted with EtOAc (20 mL x 3), washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 20:1 to 1: 1) to give dimethyl 4,5-bis(2-(benzyloxy)ethyl)phthalate as colorless oil (910 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 2H), 7.37-7.29 (m, 10H), 4.50 (s, 4H), 3.92 (s, 6H), 3.69 (t, J = 7.6 Hz, 4H), 3.04 (t, J = 7.6 Hz, 4H).

[0564] Step 3: Synthesis of dimethyl 4,5-bis(2-hydroxyethyl)phthalate (Compound 4)

[0565] Dimethyl 4,5-bis(2-(benzyloxy)ethyl)phthalate (900 mg) was dissolved in MeOH. Pd/C (150 mg, 10%) was added and the reaction mixture was stirred overnight under H_2. The mixture was filtered and concentrated to give crude dimethyl 4,5-bis(2-hydroxyethyl)phthalate (510 mg, 93% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 2H), 3.90 (t, J = 6.4 Hz, 4H), 3.89 (s, 6H), 2.99 (t, J = 6.6 Hz, 4H), 1.80 (brs, 2H).

[0566] Step 4: Synthesis of dimethyl 4,5-bis(2-((methylsulfonyl)oxy)ethyl)phthalate (Compound 5)

[0567] Dimethyl 4,5-bis(2-hydroxyethyl)phthalate (282 mg, 1.0 mmol) and Et_3N (303 mg, 3.0 mmol, 3.0 equiv) was dissolved in DCM (8 mL) and MsCl (286 mg, 2.5 mmol, 2.5 equiv) was added at 0 °C in one portion, then stirred at rt for 45 mins. TLC showed the reaction was complete. DCM was added and the reaction mixture was washed with water, aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated to give dimethyl 4,5-bis(2-((methylsulfonyl)oxy)ethyl)phthalate (430 mg) that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 2H), 4.30 (t, J = 7.2 Hz, 4H), 3.91 (s, 6H), 3.18 (t, J = 7.2 Hz, 4H), 2.96 (s, 6H).

[0568] Step 5: Synthesis of dimethyl 3-benzyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7,8-dicarboxylate (Compound 6)

[0569] Dimethyl 4,5-bis(2-((methylsulfonyl)oxy)ethyl)phthalate (430 mg) was dissolved in 1,2-dichloroethane (10 mL) and benzylamine (1.3 mL, 12 eqiv) was added. The

reaction was stirred at 50 °C for 24 h. TLC showes the reaction was complete. DCM was added and the reaction mixture was washed with water, brine, and dried. The resulting crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 10:1 to 1: 1) to give dimethyl 3-benzyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7,8-dicarboxylate (196 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 2H), 7.36-7.27 (m, 5H), 3.88 (s, 6H), 3.62 (s, 2H), 2.98-2.95 (m, 4H), 2.63-2.61 (m, 4H); LC–MS: $[M + H]^+$= 354.21

[0570] Step 6: Synthesis of 3-(tert-butyl) 7,8-dimethyl 1,2,4,5-tetrahydro-3H-benzo[d]azepine-3,7,8-tricarboxylatedimethyl (Compound 7)

[0571] Dimethyl 3-benzyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7,8-dicarboxylate (190 mg) was dissolved in MeOH, and $(Boc)_2O$ (1.1 equiv) and Pd/C (80 mg, 10% by wt) were added. The reaction mixture was stirred overnight under H_2, and the mixture was filtered and concentrated to give crude 3-(tert-butyl) 7,8-dimethyl 1,2,4,5-tetrahydro-3H-benzo[d]azepine-3,7,8-tricarboxylatedimethyl. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 2H), 7.36-7.27 (m, 5H), 3.88 (s, 6H), 3.55-3.52 (m, 4H), 2.95-2.92 (m, 4H), 1.47 (s, 9H); LC–MS: [M + H]+= 364.10

[0572] Step 6: Synthesis of tert-butyl 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3,5,6,8,9-hexahydroazepino[4,5-f]isoindole-7(1H)-carboxylate (Cpd. No. 855)

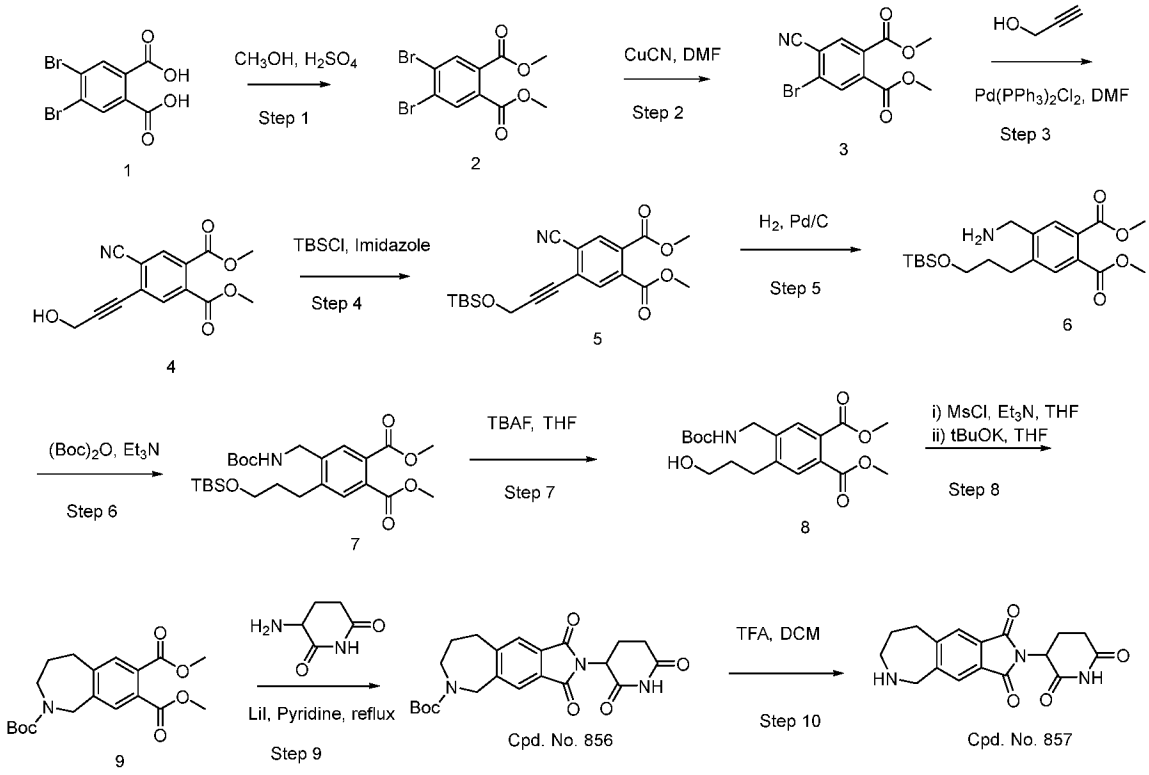
[0573] 3-(Tert-butyl) 7,8-dimethyl 1,2,4,5-tetrahydro-3H-benzo[d]azepine-3,7,8-tricarboxylate (73 mg, 0.2 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (66 mg, 0.4 mmol, 2 equiv) were dissolved in pyridine (3 mL), and LiI (268 mg, 2 mmol, 10 equiv) was added. The reaction mixture was stirred at 130 °C for 15 h. LC-MS show the reaction was complete. The solvent was removed and purified by preparative HPLC to give Cpd. No. 854. LC–MS:$[M + H]^+$= 428.30

[0574] Step 7: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione (Cpd. No. 855)

[0575] To a solution of tert-butyl 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3,5,6,8,9-hexahydroazepino[4,5-f]isoindole-7(1H)-carboxylate in DCM (2 mL) was added TFA (0.5 mL). The reaction mixture was stirred at rt for 1 h and the solvent was removed to give Cpd. No. 855 as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.01 (brs, 2H), 7.83 (s, 2H), 7.79 (s, 1H), 5.13 (dd, J = 12.8, 5.4 Hz, 1H), 3.29-3.23 (m, 8H), 2.93-2.85 (m, 1H), 2.63 – 2.51 (m, 2H), 2.09-2.03 (m, 1H); LC–MS: $[M + H]^+$= 328.21.

EXAMPLE 10

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-6,7,8,9-tetrahydroazepino[3,4-f]isoindole-1,3(2H,5H)-dione (Cpd. No. 857):



[0576] Step 1: Synthesis of Dimethyl 4,5-dibromophthalate (Compound 2)

[0577] To a solution of 4,5-dibromophthalic acid (5 g) and trimethyl orthoformate (25 mL) in MeOH (25 mL) was added conc. H_2SO_4 (2 mL) at room temperature, and the reaction was refluxed overnight. The solvent was removed under vacuum, and EtOAc (100 mL) and sat. aq. $NaHCO_3$ (20 mL) were added. The reaction mixture was extracted with EtOAc (50 mL x 3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was used in the next step without further purification. ^1H NMR (400 MHz, CDCl3) δ 3.91 (m, 6H), 7.97 (s, 2H).

[0578] Step 2: Synthesis of Dimethyl 4-bromo-5-cyanophthalate (Compound 3)

[0579] Dimethyl 4,5-dibromophthalate (1.5 g, 4.28 mmol) and copper(I) cyanide (500 mg, 5.56 mmol) were dissolved with 15 ml of anhydrous DMF and stirred at 100 °C overnight. The reaction mixture was extracted with ethyl ether three times and the organic phase was washed with cold water and brine to remove the excess DMF. Removal of the solvent followed by purification by flash chromatography on silica gel (ethyl acetate–hexane) gave dimethyl 4-bromo-5-cyanophthalate (Compound 3) in 60% yield. LC–MS: $[M + H]^+ = 297.96$.

[0580] Step 3: Synthesis of Dimethyl 4-cyano-5-(3-hydroxyprop-1-yn-1-yl)phthalate (Compound 4)

[0581] Compound 3 (1.1 g, 3.71 mmol, 1.0 eq), $Pd(PPh_3)_2Cl_2$ (263 mg, 0.371 mmol, 0.1 eq), CuI (140 mg, 0.742 nmol. 0.2 eq.), and propargyl alcohol (0.312 g, 5.57 mmol, 1.5 eq.) were dissolved with 15 mL of dry DMF, and the reaction vessel was purged with nitrogen balloon three times. Et_3N (3 mL) was added and the reaction mixture was heated to 80 °C for 2 h. The reaction mixture was extracted with ethyl ether three times and washed with cold water and brine to remove the excess DMF. Removal of the solvent followed by purification by flash chromatography on silica gel (ethyl acetate–hexane) gave dimethyl 4-cyano-5-(3-hydroxyprop-1-yn-1-yl)phthalate (Compound 4) in 70% yield. LC–MS: $[M + H]^+ = 274.06$

[0582] Step 4: Synthesis of Dimethyl 4-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-5-cyanophthalate (Compound 5)

[0583] To a solution of compound 4 (500 mg, 1.83 mmol) and imidazole (373 mg, 5.49 mmol), in dry DCM (10 mL) was added TBSCl (412 mg, 2.74 mmol) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with H_2O and extracted with DCM. The organic layers were separated and washed with H_2O, brine, dried ($MgSO_4$), and then purification by flash chromatography on silica gel (ethyl acetate–hexane) to give compound 5 as 90% yield. LC–MS: $[M + H]^+ = 388.15$

[0584] Step 5: Synthesis of Dimethyl 4-(aminomethyl)-5-(3-((tert-butyldimethylsilyl)oxy)propyl)phthalate (Compound 6)

[0585] Compound 5 (900 mg) was dissolved in MeOH and Pd/C (90 mg, 10% by wt) was added. The reaction mixture was stirred overnight under H_2. The reaction mixture was filtered and concentrated to give crude dimethyl 4-(aminomethyl)-5-(3-((tert-butyldimethylsilyl)oxy)propyl)phthalate (Compound 6). LC–MS: $[M + H]^+ = 396.21$.

[0586] Step 6: Synthesis of Dimethyl 4-(((tert-butoxycarbonyl)amino)methyl)-5-(3-((tert-butyldimethylsilyl)oxy)propyl)phthalate (Compound 7)

[0587] Crude compound 6 was dissolved in dry DCM, and Boc_2O (1.1 eq.) and Et_3N (3.0 eq.) were added. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (ethyl acetate–hexane) to give compound 7 in 60% yield. LC–MS: $[M + H]^+ = 496.27$.

[0588] Step 7: Synthesis of dimethyl 4-(((tert-butoxycarbonyl)amino)methyl)-5-(3-hydroxypropyl)phthalate (Compound 8)

[0589] Compound 7 (163 mg, 0.33 mmol) was suspended in dry THF (5 mL) and cooled in an ice bath. TBAF (1M in THF, 0.66 mL, 0.66 mmol) was added and the reaction mixture was allowed to warm to room temperature and stir for 3 h. The mixture was concentrated *in vacuo*, diluted with EtOAc, and washed with sat aq. NH_4Cl. The organic layer was concentrated to provide the crude product which was purified by flash chromatography on silica gel (ethyl acetate:hexane = 1:1) to give compound 8 in 80% yield. LC–MS: $[M + H]^+ = 382.18$.

[0590] Step 8: Synthesis of 2-(tert-butyl) 7,8-dimethyl 1,3,4,5-tetrahydro-2H-benzo[c]azepine-2,7,8-tricarboxylate (Compound 9)

[0591] Compound 8 (200 mg, 0.52 mmol) and Et_3N (131 mg, 1.3 mmol, 2.5 equiv) were dissolved in dry THF (4 mL), and MsCl (89 mg, 0.78 mmol, 1.5 equiv) was added at 0 °C in one portion. The reaction mixture was stirred at rt for 45 min. TLC showed the reaction was complete. The reaction mixture was treated with t-BuOK (1.5 ml 1 (M) THF, 3 equiv) and stirred for an additional 2 h. The reaction mixture was quenched by adding water and extracted with EtOAc. The organic layer was concentrated to provide the crude product which was purified by flash chromatography on silica gel (ethyl acetate:hexane= 1:1) to give compound 9 in 60% yield. LC–MS: $[M + H]^+ = 364.17$.

[0592] Step 9: Synthesis of tert-butyl 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3,5,7,8,9-hexahydroazepino[3,4-f]isoindole-6(1H)-carboxylate (Cpd. No. 856)

[0593] Compound 9 (70 mg, 0.2 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (66 mg, 0.4 mmol, 2 equiv) were dissolved in pyridine (3 mL) and LiI (268 mg, 2 mmol, 10 equiv) was added. The reaction mixture was stirred at 130 °C for 15 h. LC-MS show the reaction was >85% complete. The solvent was removed and the crude product purified by preparative HPLC to give Cpd. No. 856. LC–MS: $[M + H]^+ = 428.17$.

[0594] Step 10: Synthesis 2-(2,6-dioxopiperidin-3-yl)-6,7,8,9-tetrahydroazepino[3,4-f]isoindole-1,3(2H,5H)-dione (Cpd. No. 857)

[0595] Cpd. No. 856 (102.1 mg, 0.28 mmol) was added to 1 mL HCl (4M in 1,4-dioxane), and the mixture reaction mixture was stirred at room temperature for 2 h. The 1,4-dioxane was removed under reduced pressure to give Cpd. No. 857 as the HCl salt. LC–MS: $[M + H]^+ = 328.17$. ^1H NMR (400 MHz, MeOH-d_4) δ 7.88 (s, 1H), 7.79 (s, 1H), 5.11 (dd, J = 12.6, 5.4 Hz, 1H), 4.54 (s, 2H), 3.54 – 3.47 (m, 2H), 3.29 – 3.19 (m, 3H), 2.90 – 2.62 (m, 3H), 2.16 – 2.06 (m, 1H), 2.06 – 1.95 (m, 2H).

EXAMPLE 11

Biological Assays

[0596] Compounds of the Disclosure are tested for cereblon inhibition using methods known in the art. For example, Boichenko et al. describe a fluorescence resonance energy transfer (FRET)-based assay for the identification and characterization of cereblon ligands. Boichenko et al., *J. Med. Chem. 59*:770-774 (2016).

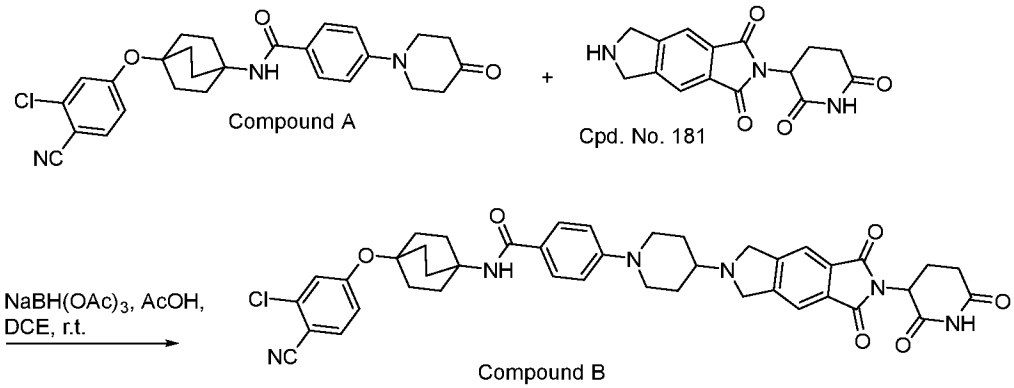
EXAMPLE 12

Synthesis of PROTAC Molecules

[0597] Compounds of the Disclosure may be used as monofunctional synthetic intermediates to prepare PROTAC molecules. PROTAC molecules comprising representative Compounds of the Disclosure are disclosed in U.S. Provisional Appl. Nos. 62/902,714, 63/024,697, and 63/024,686.

[0598] The synthesis of N-(4-(3-chloro-4-cyanophenoxy)bicyclo[2.2.2]octan-1-yl)-4-(4-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidin-1-yl)benzamide (Compound B) is shown in Scheme 1.

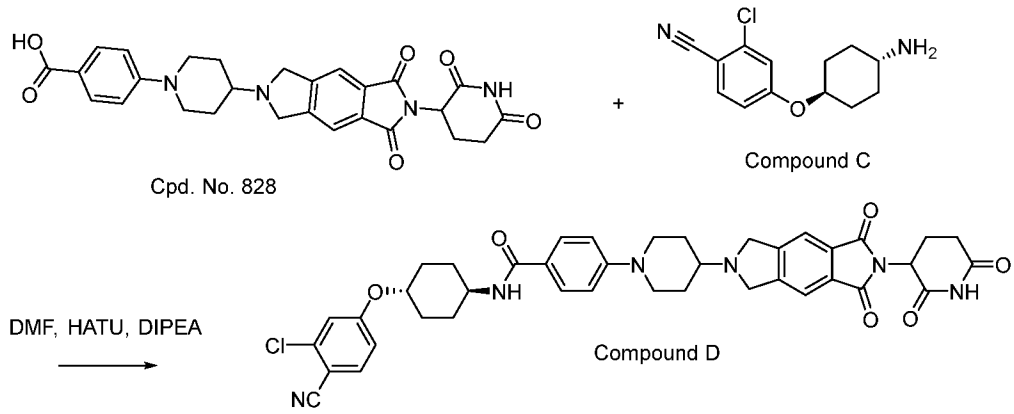
Scheme 1



[0599] To a solution of N-(4-(3-chloro-4-cyanophenoxy)bicyclo[2.2.2]octan-1-yl)-4-(4-oxopiperidin-1-yl)benzamide (Compound A) and 2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione (Cpd. No. 181) in DCE was added $NaBH(OAc)_3$ and AcOH, the reaction mixture was stirred at r.t. for 6 hours. All volatiles were removed and the residue was chromatographed on silica gel to afford Compound B. ESI-MS: 760.28.

[0600] The synthesis of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-4-(4-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidin-1-yl)benzamide (Compound D) is shown in Scheme 2.

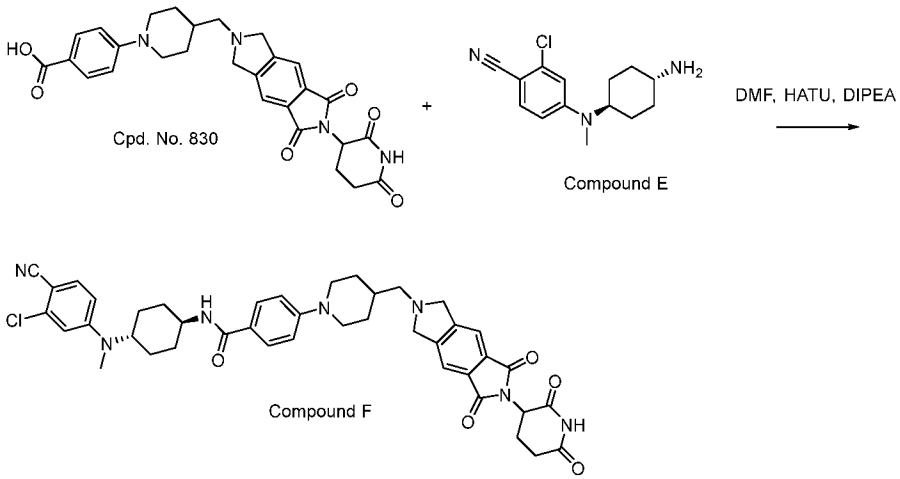
Scheme 2



[0601] Cpd. No. 828, *see* EXAMPLE 3, was dissolved in DMF, and DIPEA (3 eq) and HATU (1.3 eq) were added. Compound C was dissolved in DMF, and DIPEA (3 eq) was added. The Compound C solution was poured into the Cpd. No. 828 solution. The reaction was complete in 0.5 h. The DIPEA was removed, and H_2O and TFA (15X) were added. The product was purified by prepative HPLC to give Compound D in 39% yield. UPLC-MS 4.0 min, 735.3.

[0602] The synthesis of N-((1r,4r)-4-((3-chloro-4-cyanophenyl)(methyl)amino) cyclohexyl)-4-(4-((6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)methyl)piperidin-1-yl)benzamide (Compound F) is shown in Scheme 3.

Scheme 3



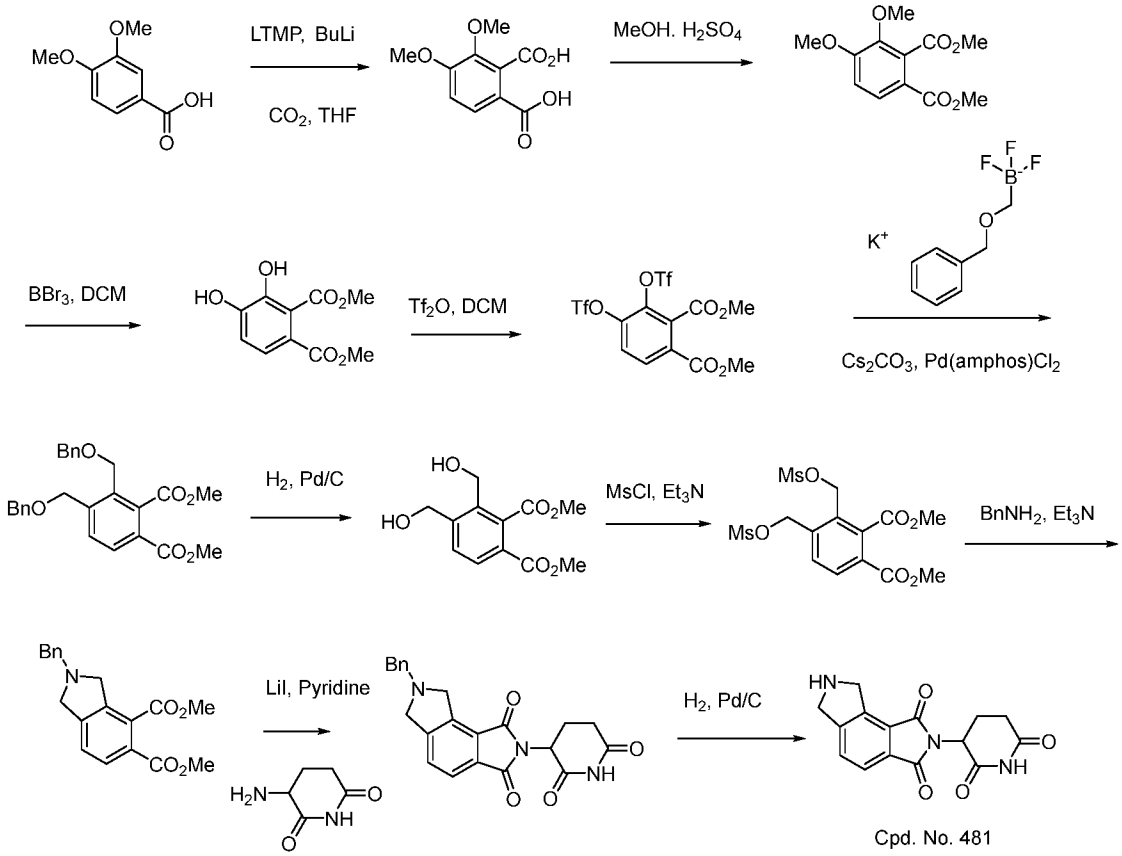
[0603] Cpd. No. 830, *see* EXAMPLE 4, was dissolved in DMF, and DIPEA (3 eq) and HATU (1.3 eq) were added. Compound E was dissolved in DMF, and DIPEA (3 eq) was added. The Compound E solution was poured into the Cpd. No. 830 solution. The reaction was complete in 0.5 h. The DIPEA was removed, and H_2O and TFA (15X) were added. The product was purified by prepative HPLC to give Compound F in 41% yield. UPLC-MS 4.1 min, 762.35.

EXAMPLE 13

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-7,8-dihydropyrrolo[3,4-e]isoindole-1,3(2H,6H)-dione (Cpd. No. 481)

[0604] The synthesis of Cpd. No. 481 is shown in Scheme 4.

Scheme 4

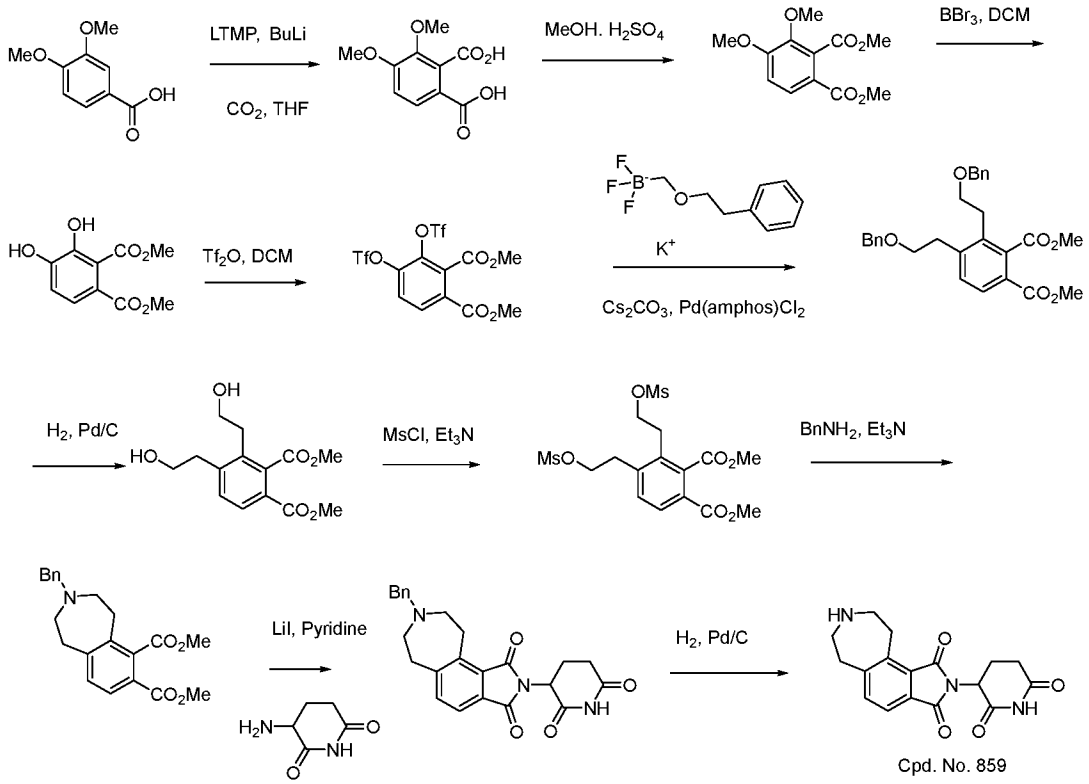


EXAMPLE 14

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-7,8,9,10-tetrahydroazepino[4,5-e]isoindole-1,3(2H,6H)-dione (Cpd. No. 859)

[0605] The synthesis of Cpd. No. 859 is shown in Scheme 5.

Scheme 5

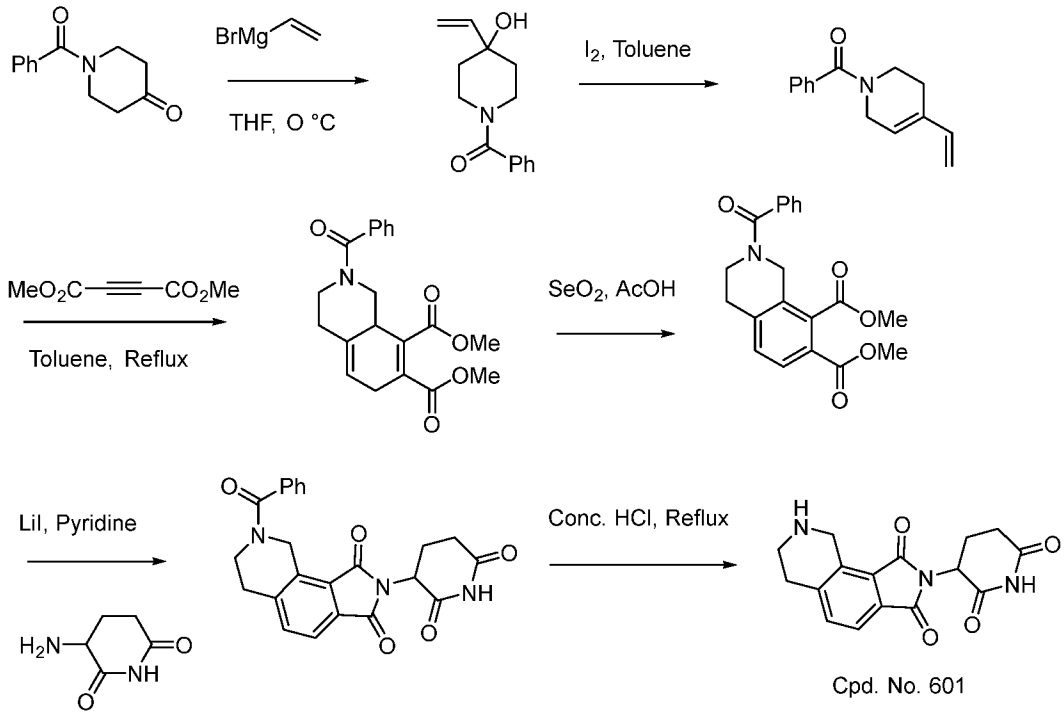


EXAMPLE 15

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,4-h]isoquinoline-1,3(2H)-dione (Cpd. No. 601)

[0606] The synthesis of Cpd. No. 601 is shown in Scheme 6.

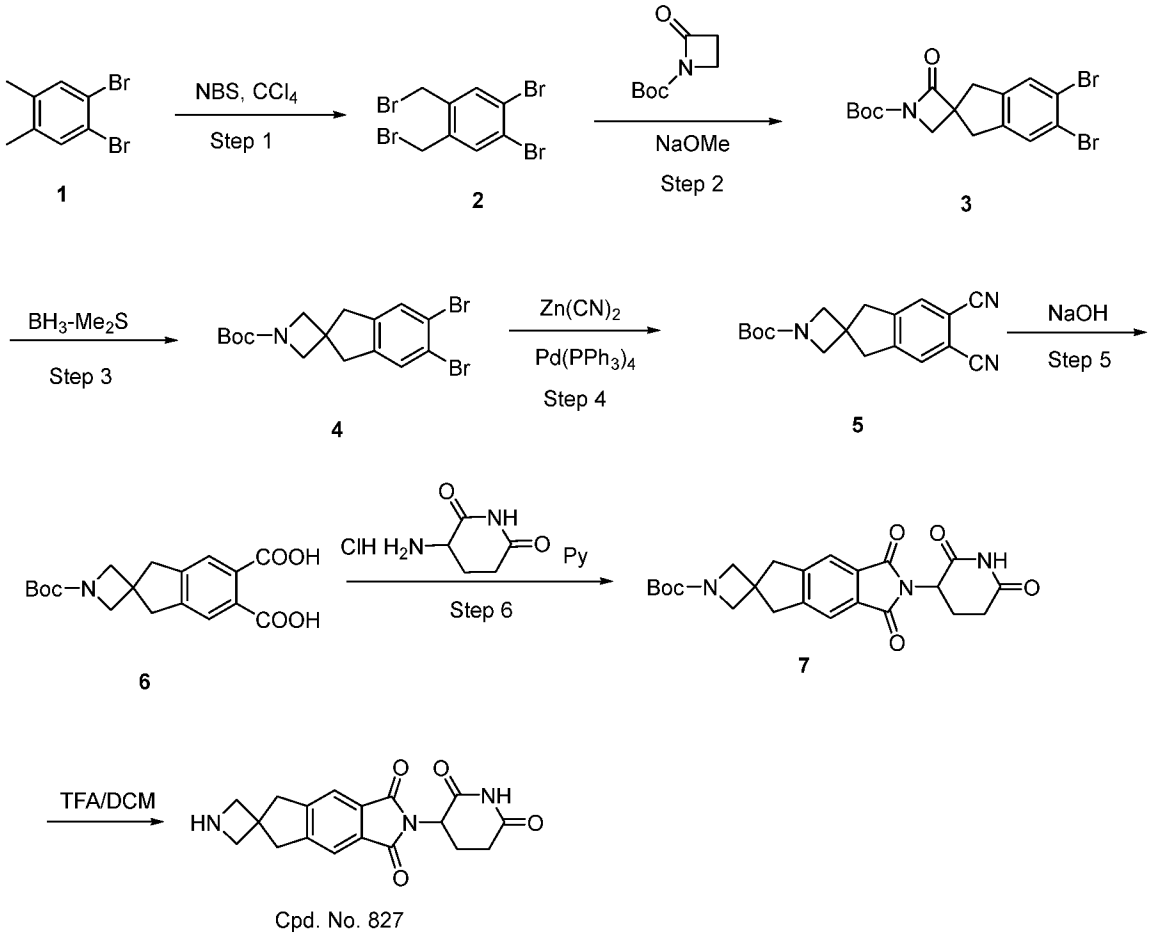
Scheme 6



EXAMPLE 16

Synthesis of 2'-(2,6-dioxopiperidin-3-yl)-5',7'-dihydro-1'H-spiro[azetidine-3,6'-cyclopenta[f]isoindole]-1',3'(2'H)-dione (Cpd. No. 827)

[0607] The synthesis of Cpd. No. 827 is shown in Scheme 7.

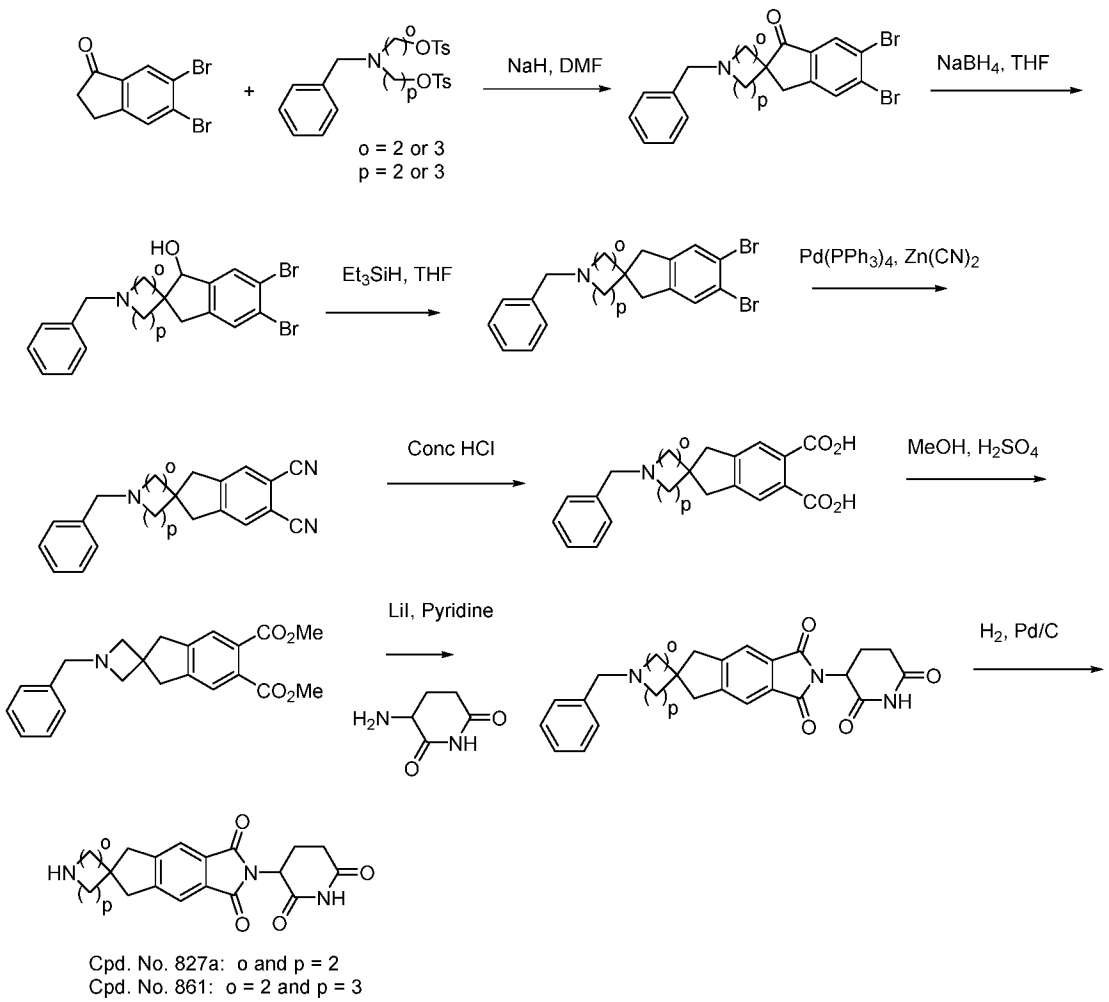


EXAMPLE 17

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]isoindole-6,4'-piperidine]-1,3(2H)-dione (Cpd. No. 827a) and 2'-(2,6-dioxopiperidin-3-yl)-5',7'-dihydro-1'H-spiro[azepane-4,6'-cyclopenta[f]isoindole]-1',3'(2'H)-dione (Cpd. No. 861)

[0608] The synthesis of Cpd. Nos. 827a and 861 are shown in Scheme 8.

Scheme 8

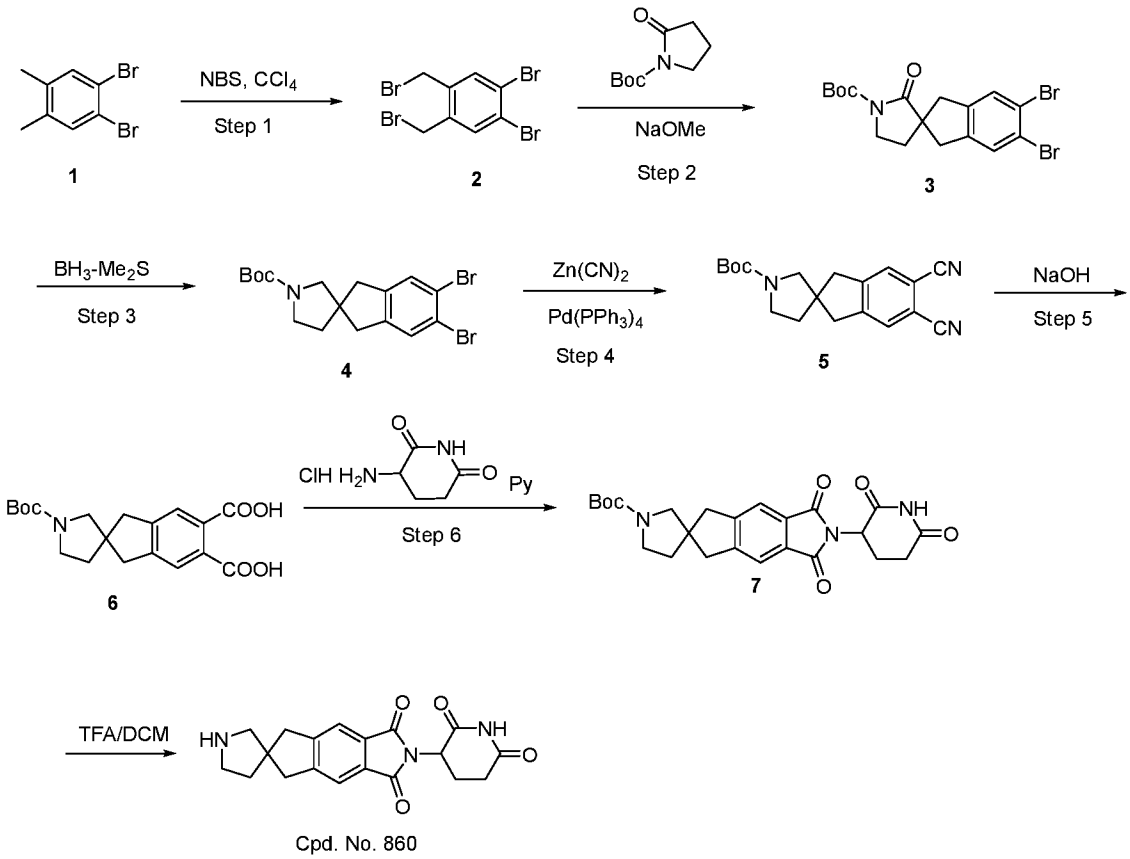


EXAMPLE 18

Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]isoindole-6,3'-pyrrolidine]-1,3(2H)-dione (Cpd. No. 860)

[0609] The synthesis of Cpd. No. 860 is shown in Scheme 9.

Scheme 9

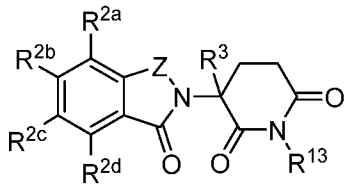


[0610] Having now fully described the methods, compounds, and compositions herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof.

[0611] All patents, patent applications, and publications cited herein are fully incorporated by reference herein in their entirety.

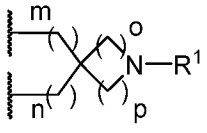
What is claimed is:

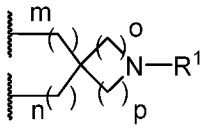
1. A compound of Formula **I**:

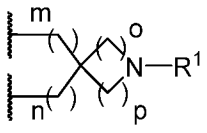


I,

wherein:

R^{2b} and R^{2c} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; or

R^{2a} and R^{2b} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; or

R^{2c} and R^{2d} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

R^3 is selected from the group consisting of hydrogen, deuterium, fluoro, and C_1-C_3 alkyl;

m is 1, 2, or 3;

n is 1, 2, or 3;

o is 1, 2, or 3;

p is 1, 2, or 3;

Z is selected from the group consisting of $-CR^{8a}R^{8b}-$ and -C(=O)-;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl,

C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$;

R^{1a} is selected from the group consisting of hydrogen, -OH, -CHO, -C(=O)OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$;

R^{1b} is selected from the group consisting of hydrogen and C_1-C_3 alkyl; or

R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a -C(=O)-;

R^4 is selected from the group consisting of $-R^{4a}$, $-OR^{4b}$, and $-NR^{4c}R^{4d}$;

R^5 is selected from the group consisting of $-R^{5a}$ and $-NR^{5b}R^{5c}$;

R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and cyano;

R^7 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and $-NR^{7a}R^{7b}$;

R^{4a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{4b} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{4c} and R^{4d} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{4c} and R^{4d} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo;

R^{5a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{5b} and R^{5c} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{7a} and R^{7b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo;

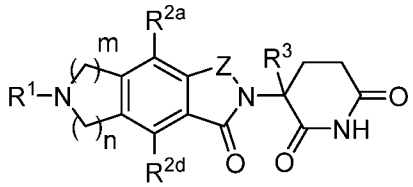
R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and C_1-C_3 alkyl; or

R^{8a} and R^{8b} taken together with the carbon atom to which they are attached from a C_3-C_6 cycloalkyl; and

R^{13} is selected from the group consisting of hydrogen and C_1-C_3 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

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



II,

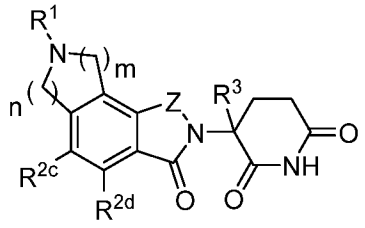
or a pharmaceutically acceptable salt or solvate thereof.

3. The compound of claim 2, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 2, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

5. The compound of any one of claims 2-4, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof.

6. The compound of claim 1 of Formula **III**:



III,

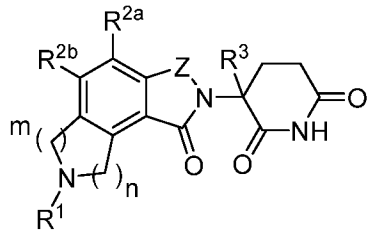
or a pharmaceutically acceptable salt or solvate thereof.

7. The compound of claim 6, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of claim 6, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of any one of claims 6-8, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of claim 1 of Formula **IV**:



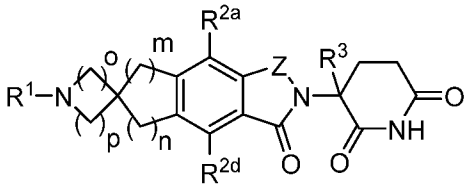
IV,

wherein Z is -$CR^{8a}R^{8b}$-, or a pharmaceutically acceptable salt or solvate thereof.

11. The compound of claim 10, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

12. The compound of claims 10 or 11, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of claim 1 of Formula **IX**:



IX,

or a pharmaceutically acceptable salt or solvate thereof.

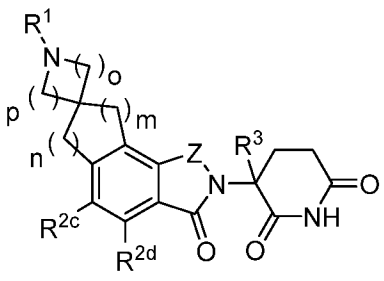
14. The compound of claim 13, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

15. The compound of claim 13, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

16. The compound of any one of claims 13-15, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof.

17. The compound of any one of claims 13-16, wherein o is 1 or 2; and p is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

18. The compound of claim 1 of Formula **X**:



X,

or a pharmaceutically acceptable salt or solvate thereof.

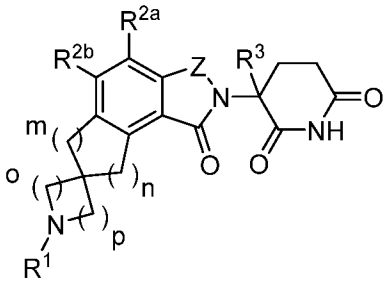
19. The compound of claim 18, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

20. The compound of claim 18, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of any one of claims 18-20, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof.

22. The compound of any one of claims 18-21, wherein o is 1 or 2; and p is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

23. The compound of claim 1 of Formula **XI**:



XI,

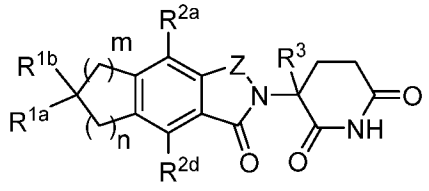
wherein Z is -$CR^{8a}R^{8b}$-, or a pharmaceutically acceptable salt or solvate thereof.

24. The compound of claim 23, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

25. The compound of claims 23 or 24, wherein R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof.

26. The compound of any one of claims 23-25, wherein o is 1 or 2; and p is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

27. The compound of claim 1 of Formula **XIV**:



XIV,

or a pharmaceutically acceptable salt or solvate thereof.

28. The compound of claim 27, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

29. The compound of claim 27, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

30. The compound of any one of claims 27-29, wherein R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, fluoro, and chloro, or a pharmaceutically acceptable salt or solvate thereof

31. The compound of any one of claims 27-30, wherein R^{1a} is selected from the group consisting of -OH, -CHO, -CH_2OH, and -C(=O)OH; and R^{1b} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

32. The compound of any one of claims 27-30, wherein R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

33. The compound of any one of claims 1-32, wherein R^3 is selected from the group consisting of hydrogen, deuterium, fluoro, and methyl, or a pharmaceutically acceptable salt or solvate thereof.

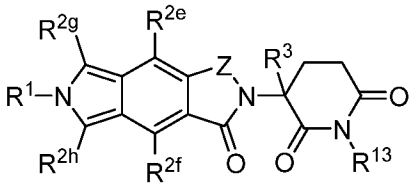
34. The compound of any one of claims 1-33, wherein m is 1, or a pharmaceutically acceptable salt or solvate thereof.

35. The compound of any one of claims 1-33, wherein m is 2, or a pharmaceutically acceptable salt or solvate thereof.

36. The compound of any one of claims 1-35, wherein n is 1, or a pharmaceutically acceptable salt or solvate thereof.

37. The compound of any one of claims 1-35, wherein n is 2, or a pharmaceutically acceptable salt or solvate thereof.

38. A compound of Formula **XVIII**:



XVIII,

wherein:

R^{2e}, R^{2f}, R^{2g}, and R^{2h} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

Z is selected from the group consisting of -$CR^{8a}R^{8b}$- and -C(=O)-;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)R^4, -$S(=O)_2R^5$, and -$C(=NR^6)R^7$;

R^3 is selected from the group consisting of hydrogen, deuterium, fluoro, and C_1-C_3 alkyl;

R^4 is selected from the group consisting of -R^{4a}, -OR^{4b}, and -$NR^{4c}R^{4d}$;

R^5 is selected from the group consisting of -R^{5a} and -$NR^{5b}R^{5c}$;

R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and cyano;

R^7 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -$NR^{7a}R^{7b}$;

R^{4a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{4b} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{4c} and R^{4d} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{4c} and R^{4d} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo;

R^{5a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{5b} and R^{5c} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{7a} and R^{7b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo;

R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and C_1-C_3 alkyl; or

R^{8a} and R^{8b} taken together with the carbon atom to which they are attached from a C_3-C_6 cycloalkyl; and

R^{13} is selected from the group consisting of hydrogen and C_1-C_3 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

39. The compound of claim 38, wherein Z is -CH_2-, or a pharmaceutically acceptable salt or solvate thereof.

40. The compound of claim 38, wherein Z is -C(=O)-, or a pharmaceutically acceptable salt or solvate thereof.

41. The compound of any one of claims 38-40, wherein R^3 is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

42. The compound of any one of claims 38-41, wherein R^{13} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

43. The compound of any one of claims 38-43, wherein R^{2e}, R^{2f}, R^{2g}, and R^{2h} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

44. The compound of any one of claims 1-26 or 33-43, wherein R^1 is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

45. The compound of any one of claims 1-26 or 33-43, wherein R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, C_1-C_6 haloalkyl, optionally substituted C_3-C_8 cycloalkyl, or a pharmaceutically acceptable salt or solvate thereof.

46. The compound of claim 45, wherein R^1 is optionally substituted C_1-C_6 alkyl, or a pharmaceutically acceptable salt or solvate thereof.

47. The compound of any one of claims 1-26 or 33-43, wherein R^1 is selected from the group consisting of (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, and aralkyl, or a pharmaceutically acceptable salt or solvate thereof.

48. The compound of claim 47, wherein R^1 is (heterocyclo)alkyl, or a pharmaceutically acceptable salt or solvate thereof.

49. The compound of any one of claims 1-26 or 33-43, wherein R^1 is selected from the group consisting of optionally substituted 4- to 8-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

50. The compound of claim 49, wherein R^1 is optionally substituted 4- to 6-membered heterocyclo.

51. The compound of any one of claims 1-26 or 33-43, wherein R^1 is $-C(=O)R^4$, or a pharmaceutically acceptable salt or solvate thereof.

52. The compound of claim 41, wherein R^4 is $-OR^{4b}$; and R^{4b} is C_1-C_6 alkyl, or a pharmaceutically acceptable salt or solvate thereof.

53. The compound of any one of claims 1-26 or 33-43, wherein R^1 is $-S(=O)_2R^5$, or a pharmaceutically acceptable salt or solvate thereof.

54. The compound of any one of claims 1-26 or 33-43, wherein R^1 is $-C(=NR^6)R^7$, or a pharmaceutically acceptable salt or solvate thereof.

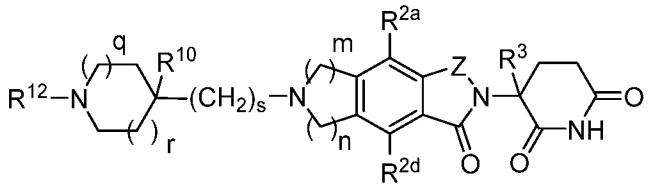
55. The compound of claim 2 that is any one or more of the compounds of Table 1, or a pharmaceutically acceptable salt or solvate thereof.

56. The compound of claim 6 that is any one or more of the compounds of Table 2, or a pharmaceutically acceptable salt or solvate thereof.

57. The compound of claim 10 that is any one or more of the compounds of Table 3, or a pharmaceutically acceptable salt or solvate thereof.

58. The compound of claim 27 that is any one or more of the compounds of Table 8, or a pharmaceutically acceptable salt or solvate thereof.

59. The compound of claim 1 of Formula **XII**:



XII,

wherein:

q and r are independently 0, 1, or 2;

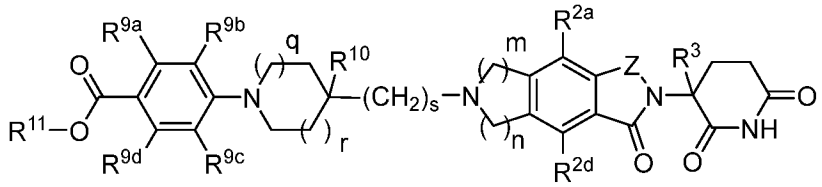
s is 0 or 1;

R^{10} is selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; and

R^{12} is selected from the group consisting of hydrogen, optionally substituted heterocylo, and optionally substituted phenyl,

or a pharmaceutically acceptable salt or solvate thereof.

60. The compound of claim 53 of Formula **XIII**:



XIII,

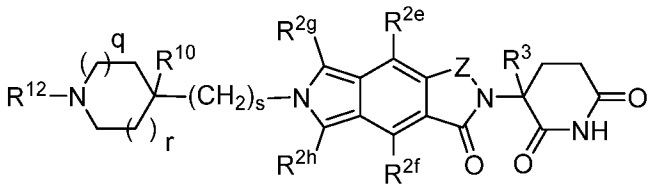
wherein:

R^{9a}, R^{9b}, R^{9c}, and R^{9d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and C_1-C_3 alkoxy; and

R^{11} is selected from the group consisting of hydrogen and C_1-C_6 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

61. The compound of claim 38 of Formula **XXI**:



XXI,

wherein:

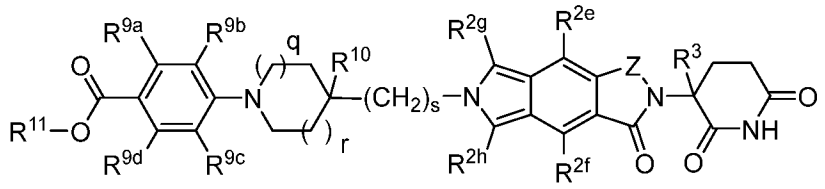
q and r are independently 0, 1, or 2;

s is 0 or 1;

R^{10} is selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; and

R^{12} is selected from the group consisting of hydrogen, optionally substituted heterocylo, and optionally substituted phenyl, or a pharmaceutically acceptable salt or solvate thereof.

62. The compound of claim 61 of Formula **XXII**:



XXII,

wherein:

R^{9a}, R^{9b}, R^{9c}, and R^{9d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and C_1-C_3 alkoxy; and

R^{11} is selected from the group consisting of hydrogen and C_1-C_6 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

63. A pharmaceutical composition comprising the compound of any one of claims 1-62, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

64. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-62, or a pharmaceutically acceptable salt or solvate thereof.

65. The method of claim 64, wherein the cancer is any one or more of the cancers of Table 5.

66. The method of claims 64 or 65 further comprising administering a therapeutically effective amount of an optional therapeutic agent useful in the treatment of cancer.

67. The pharmaceutical composition of claim 63 for use in treating cancer.

68. The pharmaceutical composition of claim 67, wherein the cancer is any one or more of the cancers of Table 5.

69. A compound of any one of claims 1-62, or a pharmaceutically acceptable salt or solvate thereof, for use in treating of cancer.

70. The compound for use of claim 69, wherein the cancer is any one or more of the cancers of Table 5.

71. Use of a compound of any one of claims 1-62, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treatment of cancer.

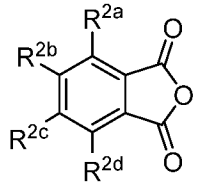
72. The use of claim 71, wherein the cancer is any one or more of the cancers of Table 5.

73. A method of inhibiting CRBN ubiquitination within a cell of a subject in need thereof, the method comprising administering to the subject a compound of any one of claims 1-62, or a pharmaceutically acceptable salt or solvate thereof.

74. A kit comprising the compound of any one of claims 1-62, 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.

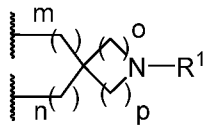
75. The kit of claim 74, wherein the cancer is any one or more of the cancers of Table 4.

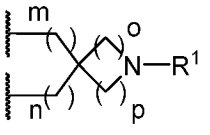
76. A compound of Formula **VI**:

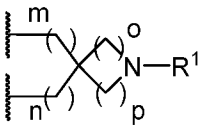


VI,

wherein:

R^{2b} and R^{2c} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2a} and R^{2d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; or

R^{2a} and R^{2b} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2c} and R^{2d} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy; or

R^{2c} and R^{2d} are taken together to form a $-(CH_2)_m-N(R^1)-(CH_2)_n-$ radical, a $-(CH_2)_m-C(R^{1a})(R^{1b})-(CH_2)_n-$ radical, or a  radical; and R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

m is 1, 2, or 3;

n is 1, 2, or 3;

o is 1, 2, or 3;

p is 1, 2, or 3

R^1 is selected from the group consisting optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$;

R^{1a} is selected from the group consisting of hydrogen, -OH, -CHO, -C(=O)OH, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally

substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$;

R^{1b} is selected from the group consisting of hydrogen and C_1-C_3 alkyl; or

R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a -C(=O)-;

R^4 is selected from the group consisting of $-R^{4a}$, $-OR^{4b}$, and $-NR^{4c}R^{4d}$;

R^5 is selected from the group consisting of $-R^{5a}$ and $-NR^{5b}R^{5c}$;

R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and cyano;

R^7 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and $-NR^{7a}R^{7b}$;

R^{4a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{4b} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{4c} and R^{4d} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{4c} and R^{4d} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo;

R^{5a} is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl;

R^{5b} and R^{5c} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl,

optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; and

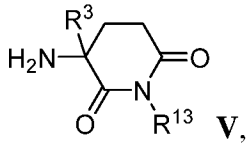
R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{7a} and R^{7b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo,

or a salt or solvate thereof.

77. A method of making a compound of claim 1, wherein the method comprising:

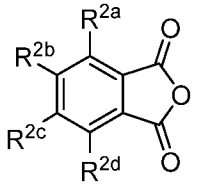
(i) reacting a compound of Formula **V**:



V,

or a salt thereof;

with compound of Formula **VI**:



VI,

in a solvent, wherein Z is -C(=O)-; and R^1 is selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, C_1-C_6 haloalkyl, (hydroxy)alkyl, (amino)alkyl, (alkoxy)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, aralkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 4- to 10-membered heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^4$, $-S(=O)_2R^5$, and $-C(=NR^6)R^7$.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/048186

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07D401/04 C07D471/04 C07D471/10 C07D487/04
C07D487/10 A61K31/454 A61K31/4545
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2018/215731 A1 (CREW ANDREW P [US] ET AL) 2 August 2018 (2018-08-02) claims 1,2,21,26,33,34	1-77
A	WO 2005/028436 A2 (US GOV HEALTH & HUMAN SERV [US]; GREIG NIGEL H [US] ET AL.) 31 March 2005 (2005-03-31) Scheme 1 on page 30, Scheme 2 on page 32; claims 1,38,43	1-77
X	EP 1 566 378 A1 (MARUISHI PHARMA [JP]) 24 August 2005 (2005-08-24) Reference Example 5(c) on page 18, Reference Example 6 on page 19	76

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 October 2020	21/10/2020

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/048186

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAO M ET AL: "Synthesis and structure-activity relationships of novel poly(ADP-ribose) polymerase-1 inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 16, no. 4, 15 February 2006 (2006-02-15), pages 938-942, XP027965785, ISSN: 0960-894X [retrieved on 2006-02-15] anhydride precursor of compound 16 in Scheme 5 on page 940	76
X	JP 2001 183770 A (KONISHIROKU PHOTO IND) 6 July 2001 (2001-07-06) compound 1-5 on page 6	76
X	J. E. BALDWIN ET AL: "332. The nonadrides. Part IV. The constitution and stereochemistry of byssochlamic acid", JOURNAL OF THE CHEMICAL SOCIETY, 1 January 1965 (1965-01-01), page 1787, XP055737997, ISSN: 0368-1769, DOI: 10.1039/jr9650001787 compound XIII on page 1790	76
X	ROOHOLLAH KAZEM SHIROODI ET AL: "Stereocontrolled 1,3-Phosphatyloxy and 1,3-Halogen Migration Relay toward Highly Functionalized 1,3-Dienes", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 134, no. 16, 12 April 2012 (2012-04-12), pages 6928-6931, XP055738027, US ISSN: 0002-7863, DOI: 10.1021/ja301243t compound 11 in Scheme 2	76
X,P	WO 2020/160196 A1 (FOGHORN THERAPEUTICS INC [US]) 6 August 2020 (2020-08-06) compounds D176 to D182 on pages 151 and 152; page 233, paragraph 5; claims 180,203,206,349	1,2,4-6, 8-10,12, 63-72, 74,75

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/048186

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