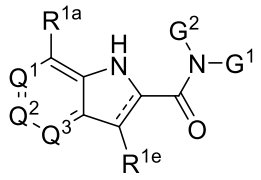
Claims

1. A compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof; for use in a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of:

(a) compound of Formula **I**:



I,

wherein:

R^{1a} is selected from the group consisting of halogen, alkyl, alkoxy, cycloalkyl, (hydroxy)alkyl, and (cycloalkyl)alkyl;

Q^1 is selected from the group consisting of -C(R^{1b})= and –N=;

Q^2 is selected from the group consisting of -C(R^{1c})= and –N=;

Q^3 is selected from the group consisting of -C(R^{1d})= and –N=;

provided that at least one of Q^1, Q^2, or Q^3 is -C(R^{1b})=, -C(R^{1c})=, or -C(R^{1d})=, respectively;

R^{1b}, R^{1c}, and R^{1d} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, (hydroxy)alkyl, and alkoxy;

R^{1e} is selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, (hydroxy)alkyl, and (cycloalkyl)alkyl;

=== is a single or double bond;

G^1 is selected from the group consisting of: optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclo; optionally substituted cycloalkyl; (aryl)alkyl; (heteroaryl)alkyl; (heterocyclo)alkyl; (amino)(aryl)alkyl; (heteroaryl)(aryl)alkyl; (heteroaryl)(heterocyclo)alkyl; (heteroaryl)(carboxamido)alkyl; (heteroaryl)(cycloalkyl)alkyl; (aryl)(alkoxycarbonyl)alkyl; (cycloalkyl)alkyl; (heteroaryl)(amino)alkyl; (cycloalkyl)(alkoxycarbonyl)alkyl; (heteroaryl)(alkoxycarbonyl)alkyl; (heterocyclo)(cycloalkyl)alkyl; (aryl)(cycloalkyl)alkyl; (aryl)(hydroxy)alkyl; (cycloalkyl)(hydroxy)alkyl; (hydroxy)alkyl; optionally substituted alkyl; (aryl)(haloalkyl)alkyl; (cycloalkyl)(haloalkyl)alkyl; (hydroxy)(haloalkyl)alkyl; and (alkoxycarbonyl)(haloalkyl)alkyl; and

G^2 is selected from the group consisting of hydrogen and alkyl; or

G^1 and G^2 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclo,

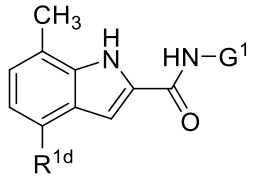
or a pharmaceutically acceptable salt or solvate thereof; and

(b) a Second Therapeutic Agent,

wherein:

the Second Therapeutic Agent comprises one or more BTK inhibitors, one or more anti-CD20 monoclonal antibodies, one or more alkylating agents, one or more topoisomerase II inhibitors, one or more vinca alkaloids, one or more platinum-based drugs, one or more nucleoside anticancer agents, one or more PI3K inhibitors, one or more CDK4/6 inhibitors, one or more CARM1 inhibitors, one or more inhibitors of enzymes of DNA damage repair, one or more SYK inhibitors, or one or more MEK inhibitors, or a combination thereof.

2. The compound for use according to claim 1, wherein the compound is a compound of Formula **II**:

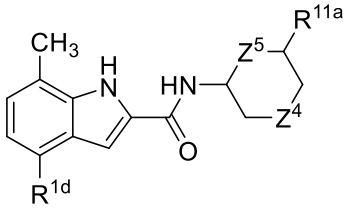


II,

or a pharmaceutically acceptable salt or solvate thereof; AND/OR

wherein G^1 is selected from the group consisting of: optionally substituted C_6-C_{10} aryl; optionally substituted 5- to 9-membered heteroaryl; optionally substituted 3- to 10-membered heterocyclo; optionally substituted C_6-C_8 cycloalkyl; (5- to 9-membered heteroaryl)C_1-C_6 alkyl; (5- to 9-membered heteroaryl)(C_{6-10} aryl)C_1-C_4 alkyl; (5- to 9-membered heteroaryl heteroaryl)(C_3-C_6 cycloalkyl)C_1-C_4 alkyl; and (C_3-C_6 cycloalkyl)C_1-C_4 alkyl, or a pharmaceutically acceptable salt or solvate thereof.

3. The compound for use according to claim 2, wherein the compound is a compound of Formula **IV**:



IV,

wherein:

Z^4 is selected from the group consisting of -O-, -C(R^{28a})(R^{28b})-, and -N(R^{23})-; or Z^4 is absent;

Z^5 is selected from the group consisting of -CH_2- and -CH_2CH_2-;

R^{11a} is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclo, optionally substituted heteroaryl, and -N(R^{12b})C(=O)R^{13c};

R^{12b} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, and heterocyclo, (C_1-C_4 alkoxy)C_1-C_4 alkyl, and (hydroxy)C_1-C_4 alkyl; and

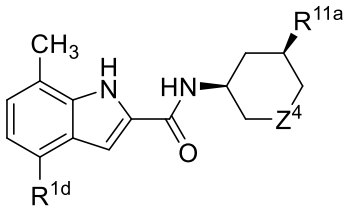
R^{13c} is selected from the group consisting of alkyl, haloalkyl, alkoxy, (alkoxy)alkyl, (hydroxy)alkyl, (cyano)alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocycle, amino, (amino)alkyl, (C_3-C_6 cycloalkyl)oxy, and (4- to 8-membered heterocyclo)oxy;

R^{23} is selected from the group consisting of hydrogen and C_1-C_4 alkyl; and

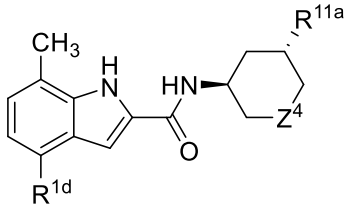
R^{28a} and R^{28b} are independently selected from the group consisting of hydrogen, alkyl, and halo;,

or a pharmaceutically acceptable salt or solvate thereof.

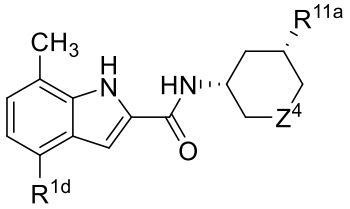
4. The compound for use according to claim 3, wherein the compound is a compound of Formula **IV-A, IV-B, IV-C, or IV-D**:



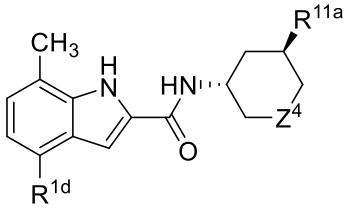
IV-A,



IV-B,



IV-C,



IV-D,

or a pharmaceutically acceptable salt or solvate thereof.

5. The compound for use according to claims 3 or 4, wherein:

R^{11a} is selected from the group consisting of:

(A) unsubstituted 4- to 14-membered heterocyclo;

(B) substituted 4- to 14-membered heterocyclo having one, two or three substituents independently selected from the group consisting of:

(i) $-N(R^{12a})C(=O)R^{13a}$; (ii) $-C(=O)R^{13b}$; (iii) C_1-C_4 alkyl; (iv) (C_1-C_4 alkoxy)C_1-C_4 alkyl; (v) (hydroxy)C_1-C_4 alkyl; (vi) C_1-C_4 haloalkyl; (vii) amino; (vii) hydroxy; (viii) $-N(R^{12a})S(=O)_2R^{24}$; (ix) $-S(=O)_2R^{24}$; (x) unsubstituted C_3-C_6 cycloalkyl; (xi) substituted C_3-C_6 cycloalkyl having one or two substituents independently selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, amino, and (amino)C_1-C_4 alkyl; (xii) unsubstituted 4- to 14-membered heterocyclo; and substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl; (xiii) $-C(=N-R^{60})R^{61}$; and(xiv) $-C(=C-NO_2)R^{64}$;

(C) unsubstituted 5- to 10-membered heteroaryl;

(D) substituted 5- or 6-membered heteroaryl having one, two, three, or four substituents independently selected from the group consisting of halo and C_1-C_4 alkyl;

(E) C_1-C_6 alkyl; and

(F) -N(R^{12b})C(=O)R^{13c};

R^{12a} and R^{12b} are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, (C_1-C_4 alkoxy)C_1-C_4 alkyl, and (hydroxy)C_1-C_4 alkyl;

R^{13a}, R^{13b}, and R^{13c} are each independently selected from the group consisting of (A) C_1-C_6 alkyl; (B) C_1-C_6 haloalkyl; (C) unsubstituted C_3-C_6 cycloalkyl; (D) C_1-C_6 alkoxy; (E) (C_1-C_4 alkoxy)C_1-C_4 alkyl; (F) (hydroxy)C_1-C_4 alkyl; (G) (cyano)alkyl; (H) unsubstituted C_6-C_{10} aryl; (I) substituted C_6-C_{10} aryl, having one, two, three, or four substituents independently selected from the group consisting of halo, amino, hydroxy, and C_1-C_4 alkyl; (J) unsubstituted 5- or 6-membered heteroaryl; (K) substituted 5- or 6-membered heteroaryl having one, two, three, or four substituents independently selected from the group consisting of halo, amino, hydroxy, and C_1-C_4 alkyl; (L) unsubstituted 4- to 14-membered heterocyclo; (M) substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl; (N) amino; (O) (amino)alkyl; (P) (C_3-C_6 cycloalkyl)oxy; and (Q) (4- to 8-membered heterocyclo)oxy; and

R^{24} is selected from the group consisting of C_1-C_4 alkyl and (hydroxy)C_1-C_4 alkyl;

R^{60} is selected from the group consisting of cyano, nitro, hydroxy, C_1-C_6 alkoxy, -C(=O)R^{62}, and -S(=O)$_2R^{62}$;

R^{61} is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and -N$R^{63a}R^{63b}$;

R^{62} is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and -N$R^{63a}R^{63b}$;

R^{63a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

R^{63b} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl; or

R^{63a} and R^{63b} taken together with the nitrogen atom to which they are attached form a 4- to 6-membered optionally substituted heterocyclo;

R^{64} is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and -N$R^{63c}R^{63d}$;

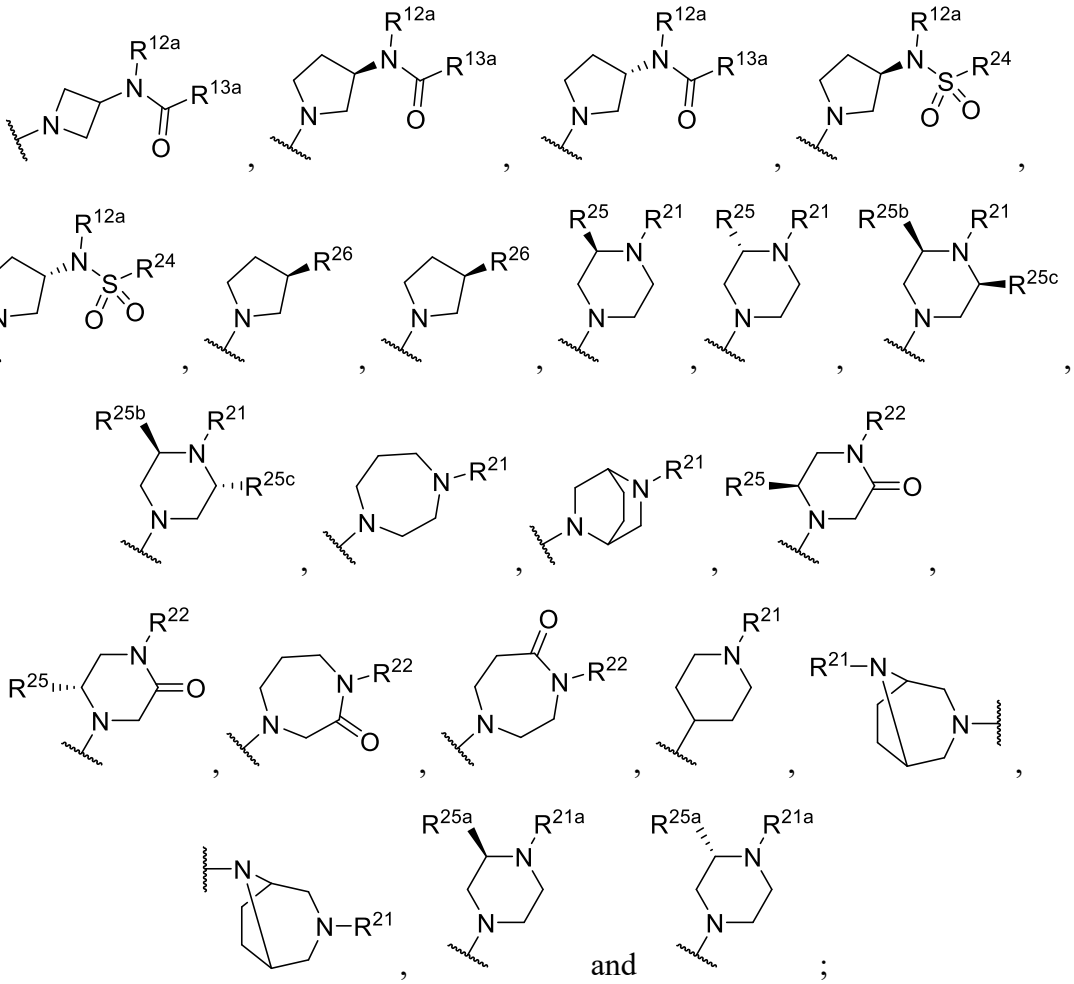
R^{63c} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

R^{63d} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl; or

R^{63c} and R^{63d} taken together with the nitrogen atom to which they are attached form a 4- to 6-membered optionally substituted heterocyclo, or a pharmaceutically acceptable salt or solvate thereof.

6. The compound for use according to claim 5, wherein:

(i) R^{11a} is a substituted 4- to 14-membered heterocyclo selected from the group consisting of:


and ;

R^{12a} is selected from the group consisting of hydrogen, C_1-C_3 alkyl, (C_1-C_4 alkoxy)C_1-C_4 alkyl; and (hydroxy)C_1-C_4 alkyl;

R^{13a} is selected from the group consisting of C_1-C_4 alkyl; amino; unsubstituted C_3-C_6 cycloalkyl; substituted C_3-C_6 cycloalkyl having one or two substituents independently selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, amino, and (amino)C_1-C_4 alkyl; (C_1-C_4 alkoxy)C_1-C_4 alkyl; (hydroxy)C_1-C_4 alkyl; unsubstituted 4- to 14-

membered heterocyclo; and substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl;

R^{13b} is selected from the group consisting of C_1-C_4 alkyl; amino; C_1-C_4 haloalkyl; C_1-C_4 alkoxy; (hydroxy)C_1-C_4 alkyl; (C_1-C_4 alkoxy)C_1-C_4 alkyl; (amino)alkyl; unsubstituted C_3-C_6 cycloalkyl; substituted C_3-C_6 cycloalkyl having one or two substituents independently selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, amino, and (amino)C_1-C_4 alkyl; unsubstituted 4- to 14-membered heterocyclo; and substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl; (C_3-C_6 cycloalkyl)oxy; and (4- to 8-membered heterocyclo)oxy;

R^{21} is selected from the group consisting of hydrogen, -C(=O)R^{13b}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, unsubstituted 4- to 14-membered heterocyclo, and -S(=O)$_2R^{24}$;

R^{22} is C_1-C_4 alkyl; unsubstituted C_3-C_6 cycloalkyl; substituted C_3-C_6 cycloalkyl having one or two substituents independently selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, amino, and (amino)C_1-C_4 alkyl; unsubstituted 4- to 14-membered heterocyclo; and substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl;

R^{24} is selected from the group consisting of C_1-C_4 alkyl and (hydroxy)C_1-C_4 alkyl;

R^{25} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

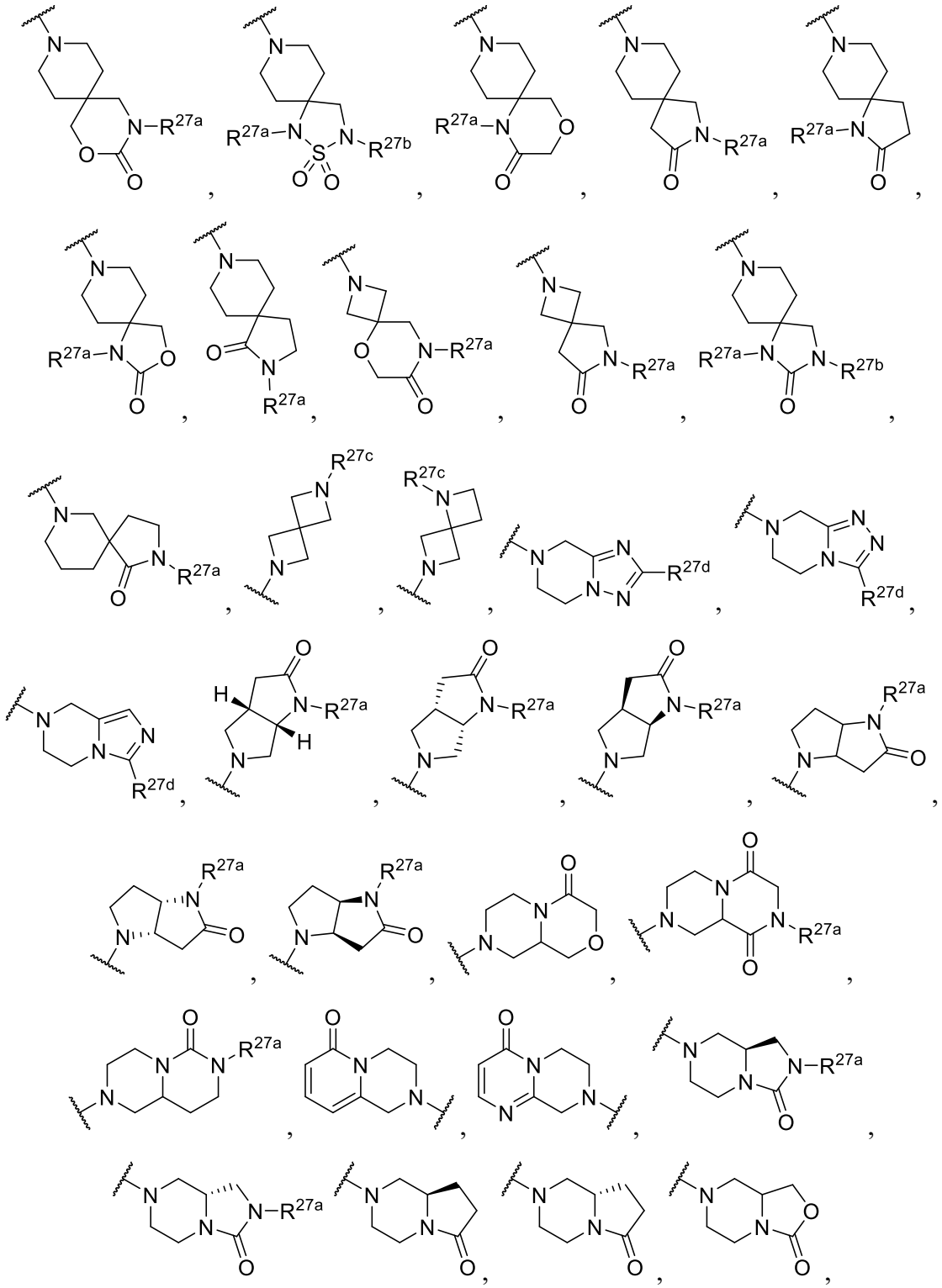
R^{25b} and R^{25c} are independently selected from the group consisting of C_1-C_4 alkyl and C_1-C_4 haloalkyl;

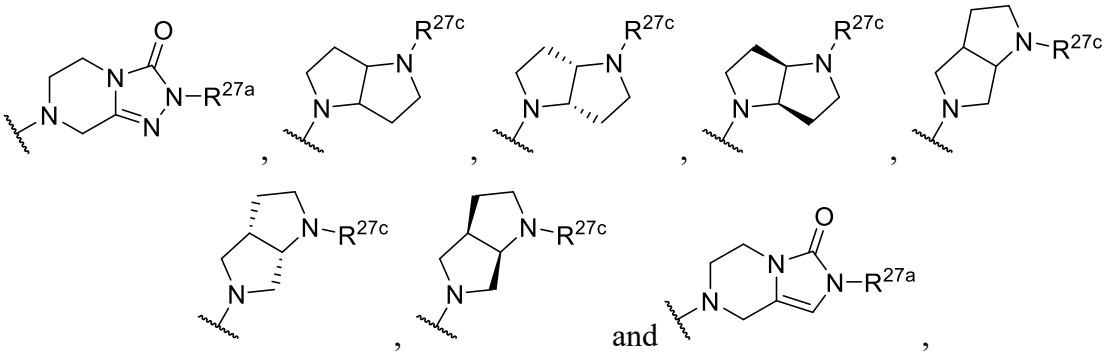
R^{26} is selected from the group consisting of unsubstituted 4- to 14-membered heterocyclo; and substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl; and

R^{21a} and R^{25a} taken together with the atoms to which they are attached form an optionally substituted 4- to 8-membered heterocyclo, or a pharmaceutically acceptable salt or solvate thereof;

OR

(ii) R^{11a} is a substituted 4- to 14-membered heterocyclo selected from the group consisting of:





R^{27a} and R^{27b} are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, (C_1-C_4 alkoxy)C_1-C_4 alkyl; and (hydroxy)C_1-C_4 alkyl;

R^{27c} is selected from the group consisting of hydrogen; -C(=O)R^{13b}; C_1-C_4 alkyl; C_1-C_4 haloalkyl; unsubstituted 4- to 14-membered heterocyclo; and substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl; and -S(=O)$_2$$R^{24}$;

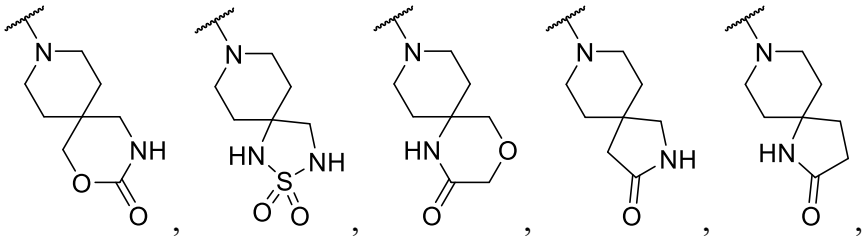
R^{27d} is selected from the group consisting of hydrogen; C_1-C_4 alkyl; and C_1-C_4 haloalkyl;

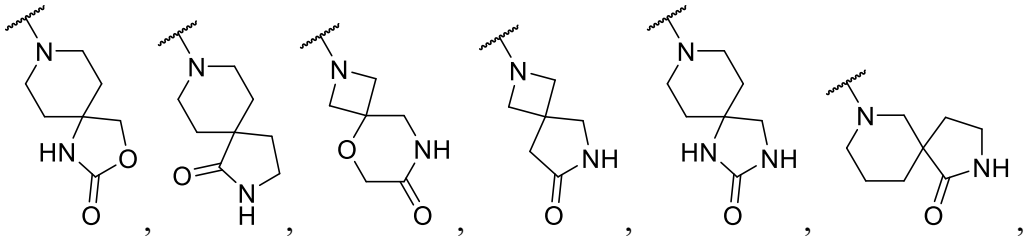
R^{13b} is selected from the group consisting of C_1-C_4 alkyl; aminoC_1-C_4 haloalkyl; C_1-C_4 alkoxy; (hydroxy)C_1-C_4 alkyl; (C_1-C_4 alkoxy)C_1-C_4 alkyl; (amino)alkyl; unsubstituted C_3-C_6 cycloalkyl; substituted C_3-C_6 cycloalkyl having one or two substituents independently selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, amino, and (amino)C_1-C_4 alkyl; unsubstituted 4- to 14-membered heterocyclo; substituted 4- to 14-membered heterocyclo having one or two substituents independently selected from the group consisting of amino, hydroxy, and C_1-C_4 alkyl; (C_3-C_6 cycloalkyl)oxy; and (4- to 8-membered heterocyclo)oxy; and

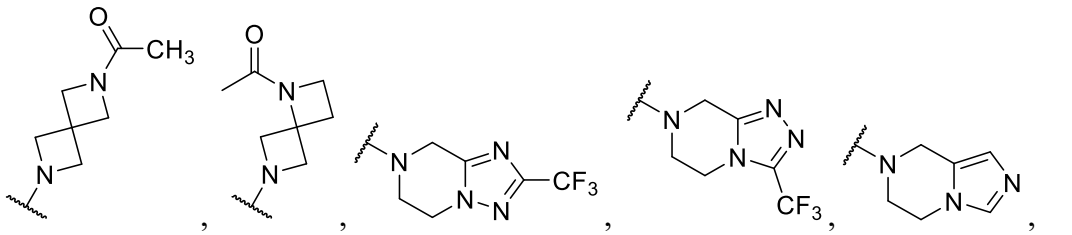
R^{24} is selected from the group consisting of C_1-C_4 alkyl and (hydroxy)C_1-C_4 alkyl, or a pharmaceutically acceptable salt or solvate thereof;

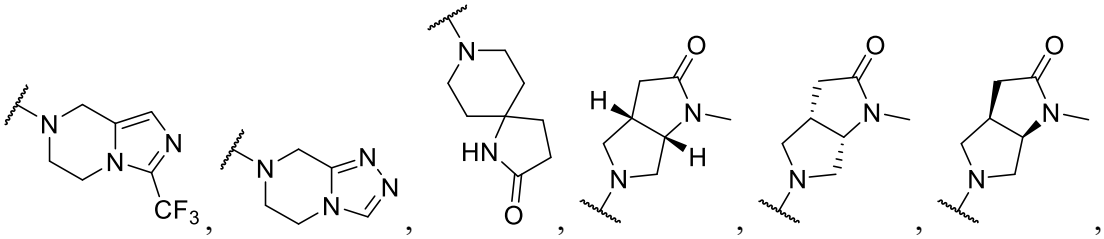
OR

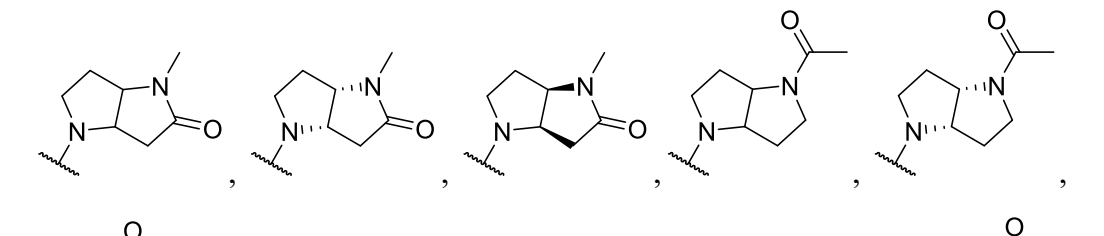
(iii) R^{11a} is a substituted 4- to 14-membered heterocyclo selected from the group consisting of:

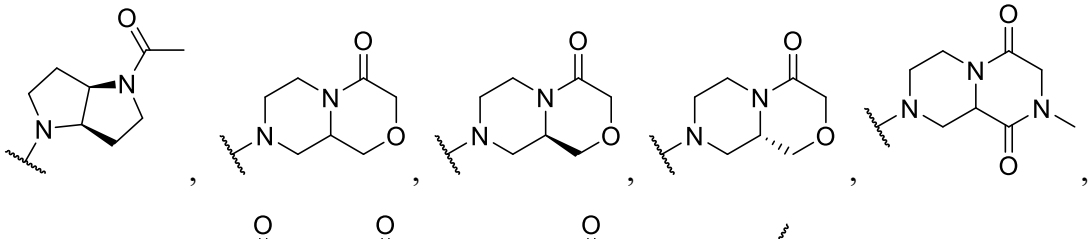


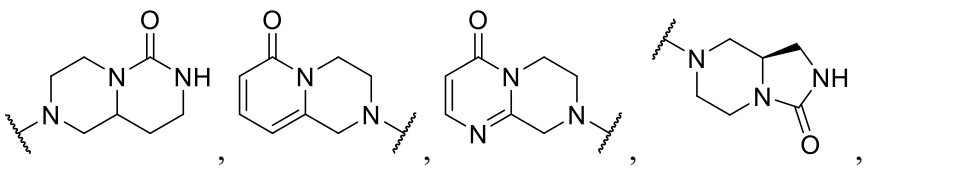


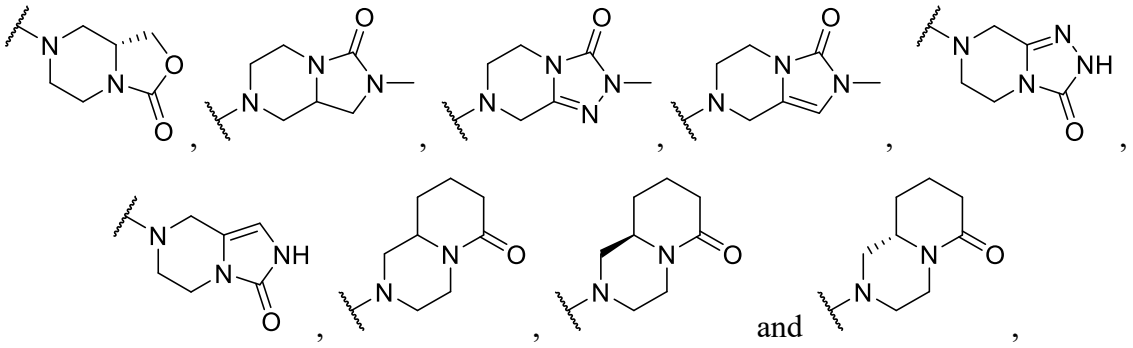






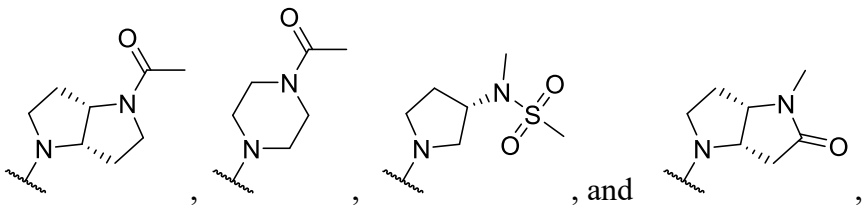






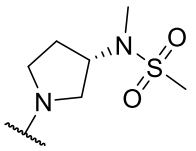
or a pharmaceutically acceptable salt or solvate thereof;
OR

(iv) R^{11a} is a substituted 4- to 14-membered heterocyclo selected from the group consisting of:



or a pharmaceutically acceptable salt or solvate thereof;
OR

(v) R^{11a} is:



or a pharmaceutically acceptable salt or solvate thereof.

7. The compound for use according to any one of claims 3-6, wherein:
Z^4 is $-CH_2-$; AND/OR

R^{1d} is fluoro, or a pharmaceutically acceptable salt or solvate thereof.

8. The compound for use according to claim 1, wherein the compound is a compound of Table 1 or Table 1B, or a pharmaceutically acceptable salt or solvate thereof.

9. The compound for use according to any one of claims 1-8, wherein the Second Therapeutic Agent comprises:

(i) a BTK inhibitor, preferably ibrutinib, acalabrutinib, or zanubrutinib; OR

(ii) an anti-CD20 monoclonal antibody, preferably rituximab; OR

(iii) a PI3K inhibitor preferably copanlisib; OR

(iv) a CDK4/6 inhibitor; preferably palbociclib; OR

(iv) a CARM1 inhibitor; preferably EZM2302; OR

(iv) an alkylating agent; preferably mafosfamide; OR

(v) a topoisomerase II inhibitor; preferably doxorubicin or etoposide; OR

(iv) a vinca alkaloid; preferably vincristine; OR

(vi) a platinum-based drug; preferably carboplatin or oxaliplatin; OR

(viii) a nucleoside anticancer agent; preferably gemcitabine; OR

(ix) a DNA repair enzyme inhibitor; preferably an ATM inhibitor, ATR inhibitor, Chk1 inhibitor, Wee1 inhibitor, RAD51 inhibitor, PARP inhibitor, or AKT inhibitor; more preferably

the ATM inhibitor is AZD0156, dactolisib, KU-55933, CP-466722, or AZD1390;

the ATR inhibitor is AZD6738 VX-803, or elimusertib;

the Chk1 inhibitor is AZD7762, rabusertib, MK-8776, CHIR-124, or PF-477736;

the Wee1 inhibitor is AZD1775;

the RAD51 inhibitor is B02 or RI-1;

the PARP inhibitor is olaparib, niraparib rucaparib, or talazoparib;

the AKT inhibitor is MK2206; OR

(x) a SYK inhibitor; preferably tamatinib, fostamatinib, R406, MNS, lanraplenib, TAK-659, entospletinib, or BAY-61-3606; OR

(ix) a MEK inhibitor; preferably trametinib, selumetinib, or merdametinib.

10. The compound for use according to any one of claims 1-9, wherein the compound is Cpd. No. 15, or a pharmaceutically acceptable salt or solvate thereof.

11. The compound for use according to any one of claims 1-10 further comprising administering a therapeutically effective amount of a Third Therapeutic Agent to the subject, wherein the Third Therapeutic Agent comprises one or more glucocorticoid receptor agonists, one or more immunomodulatory drugs, one or more proteasome inhibitors, one or more Bcl-2 inhibitors, one or more pleiotropic pathway modulators, one or more XPO1 inhibitors, one or more histone deacetylase inhibitors, one or more EZH2 inhibitors, or a combination thereof.

12. The compound for use according to claim 11, wherein the Third Therapeutic Agent comprises:

a glucocorticoid receptor agonist; preferably

(i) dexamethasone; OR

an immunomodulatory drug; preferably pomalidomide or lenalidomide; OR

(ii) a proteasome inhibitor; preferably bortezomib; OR

(iii) a Bcl-2 inhibitor; preferably venetoclax; OR

(iv) a pleiotropic pathway modulator; preferably CC-122; OR

(v) a XPO1 inhibitor; preferably selinexor; OR

(vi) a histone deacetylase inhibitor; preferably panobinostat; OR

(vii) an EZH2 inhibitor; preferably

(viii) tazemetostat.

13. The compound for use according to any one of claims 1-10, wherein the compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof, and the Second Therapeutic Agent are administered to the subject separately; OR

the compound for use according to claims 11 or 12, wherein the compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof, the Second Therapeutic Agent, and the Third Therapeutic Agent are administered to the subject separately

14. The compound for use according to any one of claims 1-13, wherein the subject in need thereof has cancer; preferably wherein the cancer is:

(i) any one or more of the cancers of Table 2; OR

(ii) a hematological cancer.

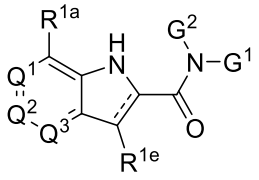
(iii) any one or more of the cancers of Table 3; or

(iv) multiple myeloma, mantle cell lymphoma, or diffuse large B-cell lymphoma; or

(v) t(4;14) multiple myeloma.

15. A kit comprising:

(a) compound of Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} is selected from the group consisting of halogen, alkyl, alkoxy, cycloalkyl, (hydroxy)alkyl, and (cycloalkyl)alkyl;

Q^1 is selected from the group consisting of -C(R^{1b})= and –N=;

Q^2 is selected from the group consisting of -C(R^{1c})= and –N=;

Q^3 is selected from the group consisting of -C(R^{1d})= and –N=;

provided that at least one of Q^1, Q^2, or Q^3 is -C(R^{1b})=, -C(R^{1c})=, or -C(R^{1d})=, respectively;

R^{1b}, R^{1c}, and R^{1d} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, (hydroxy)alkyl, and alkoxy;

R^{1e} is selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, (hydroxy)alkyl, and (cycloalkyl)alkyl;

⁻⁻⁻ is a single or double bond;

G^1 is selected from the group consisting of: optionally substituted aryl;

optionally substituted heteroaryl; optionally substituted heterocyclo; optionally substituted cycloalkyl; (aryl)alkyl; (heteroaryl)alkyl; (heterocyclo)alkyl; (amino)(aryl)alkyl; (heteroaryl)(aryl)alkyl; (heteroaryl)(heterocyclo)alkyl; (heteroaryl)(carboxamido)alkyl; (heteroaryl)(cycloalkyl)alkyl; (aryl)(alkoxycarbonyl)alkyl; (cycloalkyl)alkyl; (heteroaryl)(amino)alkyl; (cycloalkyl)(alkoxycarbonyl)alkyl; (heteroaryl)(alkoxycarbonyl)alkyl; (heterocyclo)(cycloalkyl)alkyl; (aryl)(cycloalkyl)alkyl; (aryl)(hydroxy)alkyl; (cycloalkyl)(hydroxy)alkyl; (hydroxy)alkyl; optionally substituted alkyl; (aryl)(haloalkyl)alkyl; (cycloalkyl)(haloalkyl)alkyl; (hydroxy)(haloalkyl)alkyl; and (alkoxycarbonyl)(haloalkyl)alkyl; and

G^2 is selected from the group consisting of hydrogen and alkyl; or

G^1 and G^2 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclo,

(b) a Second Therapeutic Agent,

wherein the Second Therapeutic Agent comprises one or more BTK inhibitors, one or more anti-CD20 monoclonal antibodies, one or more alkylating agents, one or

more topoisomerase II inhibitors, one or more vinca alkaloids, one or more platinum-based drugs, one or more nucleoside anticancer agents, one or more PI3K inhibitors, one or more CDK4/6 inhibitors, one or more CARM1 inhibitors, one or more inhibitors of enzymes of DNA damage repair, one or more SYK inhibitors, or one or more MEK inhibitors, or a combination thereof; and

(c) instructions for administering the compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof, and the Second Therapeutic Agent to a subject.