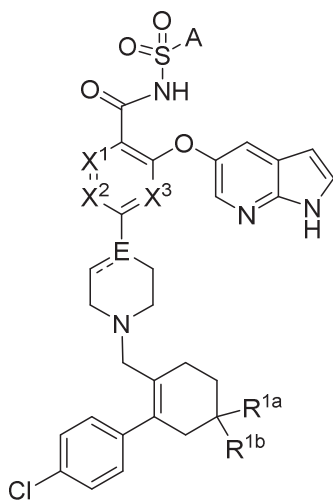


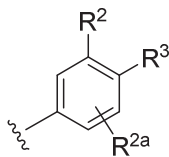
BRIEF SUMMARY ~~OF THE INVENTION~~

[00011a] In one example, the present disclosure provides a compound having Formula I-A:

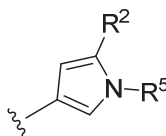


or a pharmaceutically acceptable salt or solvate thereof, wherein:

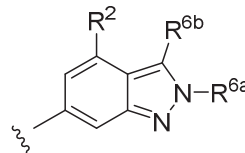
A is selected from the group consisting of:



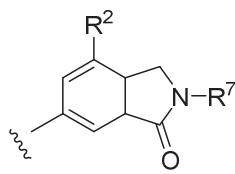
A-1



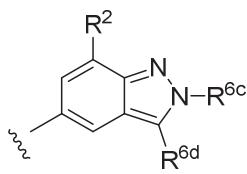
A-2



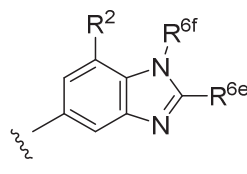
A-3



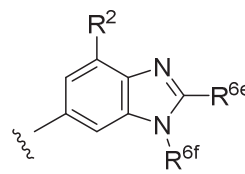
A-4



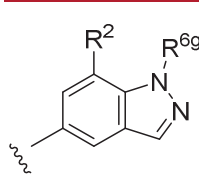
A-5



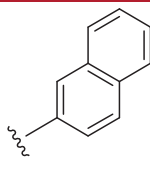
A-6



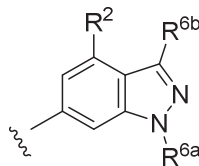
A-7



A-8



A-9



A-10

E is a carbon atom and == is a double bond; or

E is a -C(H)- and == is a single bond; or

E is a nitrogen atom and --- is a single bond;

X¹, X², and X³ are each independently selected from the group consisting of -CR⁸= and -N=;

R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a 3-, 4-, or 5-membered optionally substituted cycloalkyl; or

R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a 4- or 5-membered optionally substituted heterocyclo;

R² is selected from the group consisting of -NO₂, -SO₂CH₃, and -SO₂CF₃;

R^{2a} is selected from the group consisting of hydrogen and halogen;

R³ is selected from the group consisting of hydrogen, -CN, -C≡CH, and -N(R^{4a})(R^{4b});

R^{4a} is selected from the group consisting of optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₆ cycloalkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl;

R^{4b} is selected from the group consisting of hydrogen and C₁₋₄ alkyl;

R⁵ is selected from the group consisting of is selected from the group consisting of optionally substituted C₁₋₆ alkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl;

R^{6a}, R^{6c}, R^{6e}, R^{6f}, and R^{6g} are each independently selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₆ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl;

R^{6b} and R^{6d} are each independently selected from the group consisting of hydrogen, C₁₋₄ alkyl, and halogen;

R⁷ is selected from the group consisting of optionally substituted C₁₋₆ alkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl; and

R⁸ is selected from the group consisting of hydrogen and halogen.

[00011b] In another example, the present disclosure provides a pharmaceutical composition comprising the compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[00011c] In another example, the present disclosure provides a use of the compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a hyperproliferative disease.

[00011d] In another example, the present disclosure provides a use of the pharmaceutical composition of the disclosure in the manufacture of a medicament for treating a hyperproliferative disease.

[00011e] In another example, the present disclosure provides a kit comprising the compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or solvate thereof, to a patient having a hyperproliferative disease.

[0012] In one aspectexample, the present disclosure provides compounds represented by any one of Formulae I-A or I-VIII, below, and the pharmaceutically acceptable salts and solvates, e.g., hydrates, thereof, collectively referred to herein as "Compounds of the Disclosure."

[0013] In another aspectexample, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and one or more pharmaceutically acceptable carriers.

[0014] In another aspectexample, the present disclosure provides a method of inhibiting Bcl-2 proteins, e.g., Bcl-2, Bcl-w, Bcl-xL, Mcl-1, and Bfl-1/A1, or any combination thereof, in a subject, e.g., a human, comprising administering to the subject an effective amount of at least one Compound of the Disclosure.

[0015] In another aspectexample, the present disclosure provides methods for treating or preventing diseases, disorders, or conditions, e.g., a hyperproliferative disease, e.g., cancer, e.g., small cell lung cancer, non-Hodgkin's lymphoma (NHL), acute myelogenous leukemia (AML), chronic lymphoid (or lymphocytic) leukemia (CLL), or acute lymphoblastic leukemia (ALL), in a subject responsive to inhibition of Bcl-2 proteins, e.g., Bcl-2 and/or Bcl-xL, comprising administering to the subject a therapeutically effective amount of a Compound of the Disclosure.

[0016] In another aspectexample, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of one or more Bcl-2 proteins, e.g., Bcl-2 and/or Bcl-xL.

[0017] In another aspectexample, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of Bcl-2.

[0018] In another aspectexample, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of Bcl-xL.

[0019] In another aspectexample, the present disclosure provides a pharmaceutical composition for treating diseases, disorders, or conditions responsive to inhibition of Bcl-2 proteins, e.g., Bcl-2 and/or Bcl-xL, wherein the pharmaceutical composition comprises a therapeutically effective amount of a Compound of the Disclosure optionally admixed with one or more pharmaceutically acceptable carriers.

[0020] In another ~~aspect~~example, the present disclosure provides Compounds of the Disclosure for use in treating or preventing a disease, disorder, or condition, e.g., a hyperproliferative disease, e.g., cancer, in a subject, e.g., a human.

[0021] In another ~~aspect~~example, the present disclosure provides a Compound of the Disclosure for use in the manufacture of a medicament for treating a disease, disorder, or condition, e.g., a hyperproliferative disease, e.g., cancer, in a subject, e.g., a human.

[0022] In another ~~aspect~~example, the present disclosure provides kit comprising a Compound of the Disclosure.

[0023] In another ~~aspect~~example, the present disclosure provides a kit comprising a Compound of the Disclosure and a second therapeutic agent useful in the treatment of a disease, disorder, or condition of interest, and a package insert containing directions for use in the treatment of that disease, disorder, or condition.

[0024] In another ~~aspect~~example, 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.

[0025] Additional ~~embodiments~~examples 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~~examples and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0026] 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~~disclosure as claimed.

DETAILED DESCRIPTION OF DRAWINGS

[0027] Fig. 1 is an illustration (Western blotting analysis) showing the expression of PARP, cleaved caspase-3, and Bcl-2 in RS4;11 xenograft tumor tissues obtained from mice following administration of Compounds of the Disclosure and ABT-199.

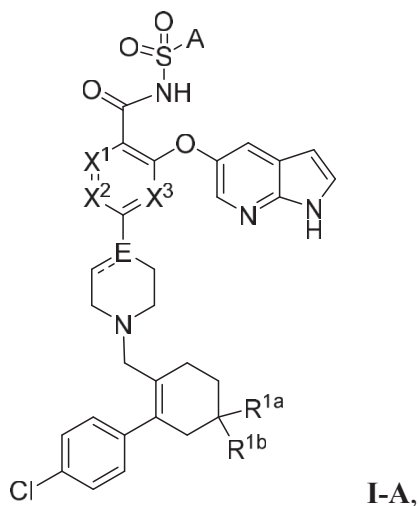
[0028] Fig. 2 is an illustration (Western blotting analysis) showing the expression of PARP and caspase-3 in RS4;11 xenograft tumor tissues obtained from mice following administration of Compounds of the Disclosure.

[0029] Fig. 3 is a line graph showing the antitumor activity of Cpd. No. 6 in the RS4;11 leukemia xenograft model.

[0030] Fig. 4 is a line graph showing the mouse weight following administration of Cpd. No. 6 in the RS4;11 leukemia xenograft model.

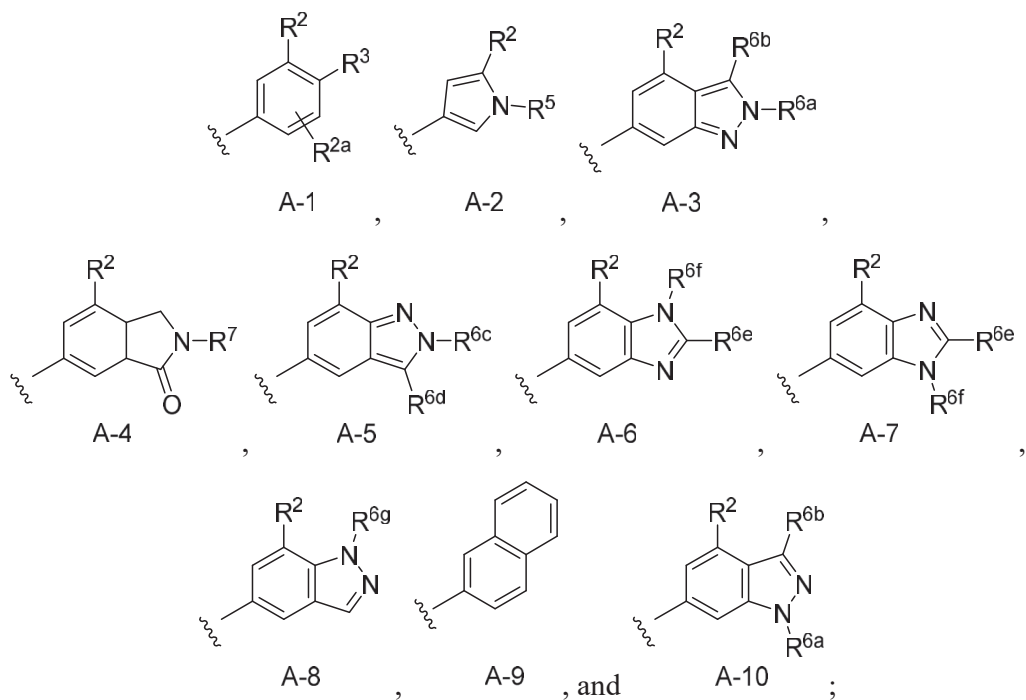
What is Claimed Is:

1. A compound having Formula **I-A**:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of:



E is a carbon atom and == is a double bond; or

E is a -C(H)- and == is a single bond; or

E is a nitrogen atom and == is a single bond;

X¹, X², and X³ are each independently selected from the group consisting of -CR⁸= and -N=;

R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a 3-, 4-, or 5-membered optionally substituted cycloalkyl; or

R^{1a} and R^{1b} taken together with the carbon atom to which they are attached form a 4- or 5-membered optionally substituted heterocyclo;

R^2 is selected from the group consisting of $-\text{NO}_2$, $-\text{SO}_2\text{CH}_3$, and $-\text{SO}_2\text{CF}_3$;

R^{2a} is selected from the group consisting of hydrogen and halogen;

R^3 is selected from the group consisting of hydrogen, $-\text{CN}$, $-\text{C}\equiv\text{CH}$, and $-\text{N}(\text{R}^{4a})(\text{R}^{4b})$;

R^{4a} is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl;

R^{4b} is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R^5 is selected from the group consisting of is selected from the group consisting of optionally substituted C_{1-6} alkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl;

R^{6a} , R^{6c} , R^{6e} , R^{6f} , and R^{6g} are each independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl;

R^{6b} and R^{6d} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and halogen;

R^7 is selected from the group consisting of optionally substituted C_{1-6} alkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl; and

R^8 is selected from the group consisting of hydrogen and halogen.

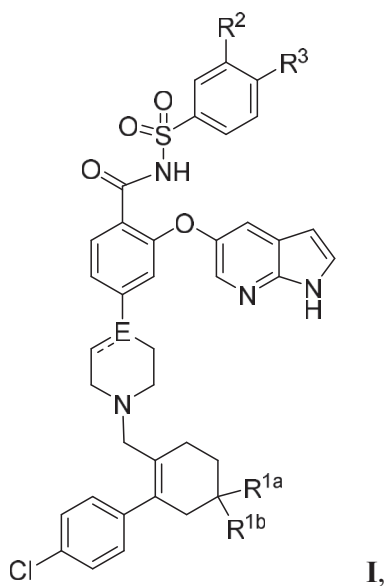
2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of A-1, A-2, A-3, A-4, A-5, A-6, A-7, A-8, and A-9;

R^{4a} is selected from the group consisting of optionally substituted C_{1-6} alkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl; and

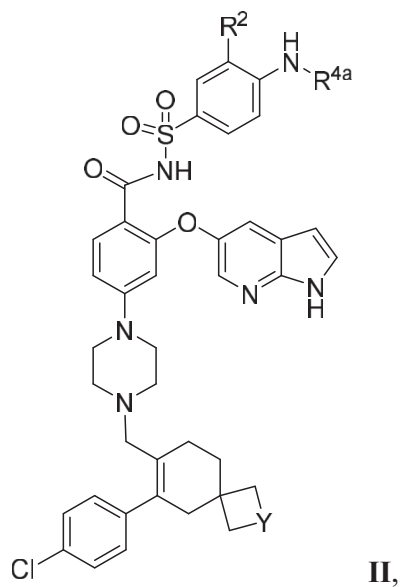
R^{6a} , R^{6c} , R^{6e} , R^{6f} , and R^{6g} are each independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, heterocyclo, heteroalkyl, (cycloalkyl)alkyl, and (heterocyclo)alkyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having Formula **I**:



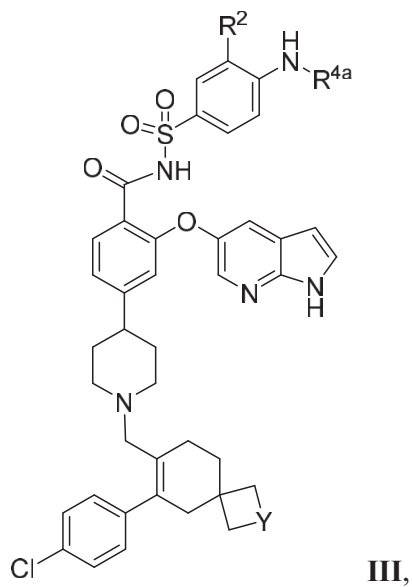
wherein R^{4a} is selected from the group consisting of C_{1-6} alkyl, optionally substituted heterocyclo, (cycloalkyl)alkyl, and (heterocyclo)alkyl.

4. The compound of claims 1 or 3, or a pharmaceutically acceptable salt or solvate thereof, having Formula **II**:



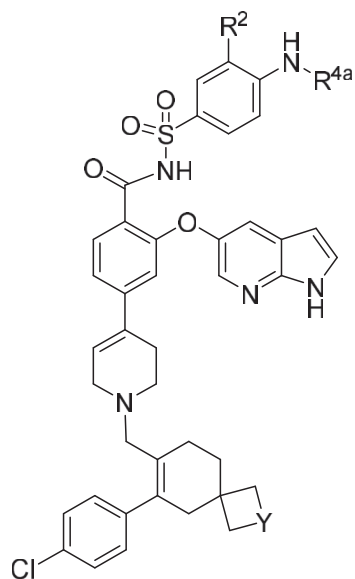
wherein Y selected from the group consisting of -CH₂- and -O-.

5. The compound of claims 1 or 3, or a pharmaceutically acceptable salt or solvate thereof, having Formula **III**:



wherein Y selected from the group consisting of -CH₂- and -O-.

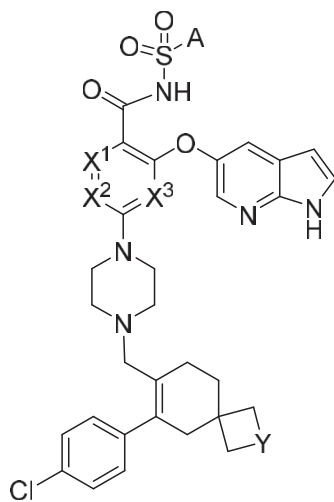
6. The compound of claims 1 or 3, or a pharmaceutically acceptable salt or solvate thereof, having Formula **IV**:



IV,

wherein Y selected from the group consisting of -CH₂- and -O-.

7. The compound of claims 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, having Formula **V**:



V,

wherein Y selected from the group consisting of -CH₂- and -O-,

8. The compound of any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-1.

9. The compound of any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-2.

10. The compound of any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-3.

11. The compound of any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-4.

12. The compound of any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-5.

13. The compound of any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-6.

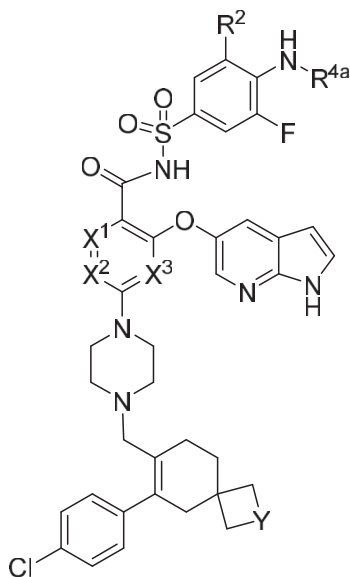
14. The compound any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-7.

15. The compound any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-8.

16. The compound any one of claims 1, 2, or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-9.

17. The compound of claims 1 or 7, or a pharmaceutically acceptable salt or solvate thereof, wherein A is A-10.

18. The compound of claim 8, or a pharmaceutically acceptable salt or solvate thereof, having Formula **VII**:



VII.

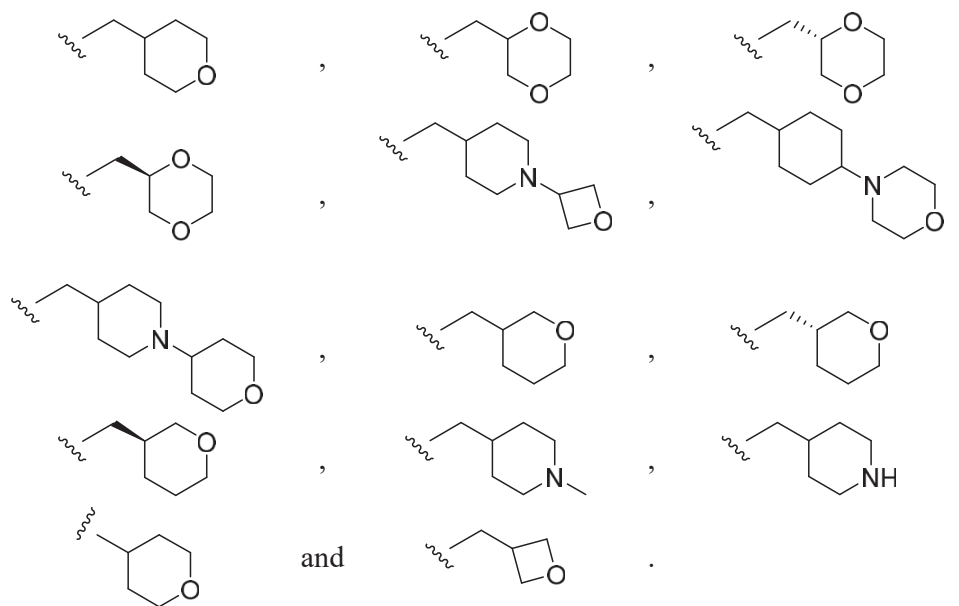
19. The compound of any one of claims 1, 2, or 6-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 , X^2 , and X^3 are each $-CH=$.
20. The compound of any one of claims 1, 2, or 6-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is $-CF=$, and X^2 and X^3 are each $-CH=$.
21. The compound of any one of claims 1, 2, or 6-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 and X^3 are each $-CH=$, and X^2 is $-CF=$.
22. The compound of any one of claims 1, 2, or 6-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 and X^2 are each $-CH=$, and X^3 is $-CF=$.
23. The compound of any one of claims 1, 2, or 6-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is $-N=$, and X^2 and X^3 are each $-CH=$.
24. The compound of any one of claims 1, 2, or 6-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 and X^3 are each $-CH=$, and X^2 is $-N=$.
25. The compound of any one of claims 1, 2, or 6-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 and X^2 are each $-CH=$, and X^3 is $-N=$.

26. The compound of any one of claims 4-25, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -O-.

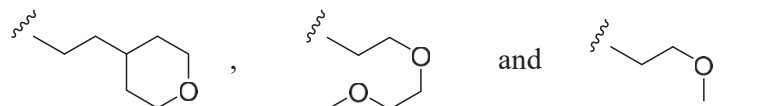
27. The compound of any one of claims 4-25, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -CH₂-.

28. The compound of any one of claims 1-15 or 17-27, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is -NO₂.

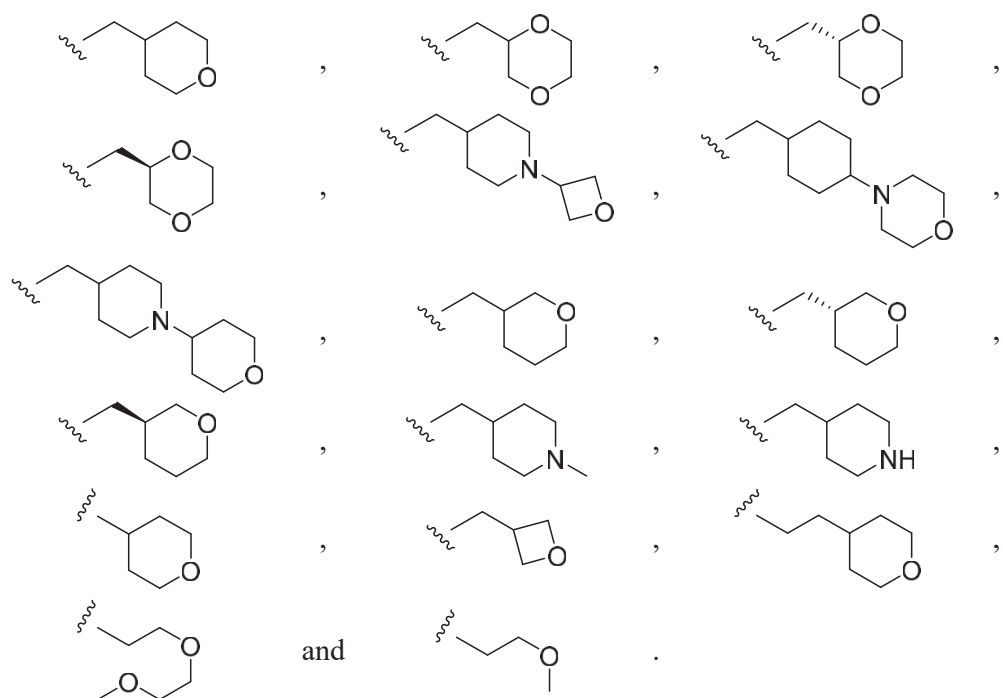
29. The compound of any one of claims 1-8 or 17-28, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{4a} is selected from the group consisting of:



30. The compound of claims 1-8 or 17-28, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{4a} is selected from the group consisting of:



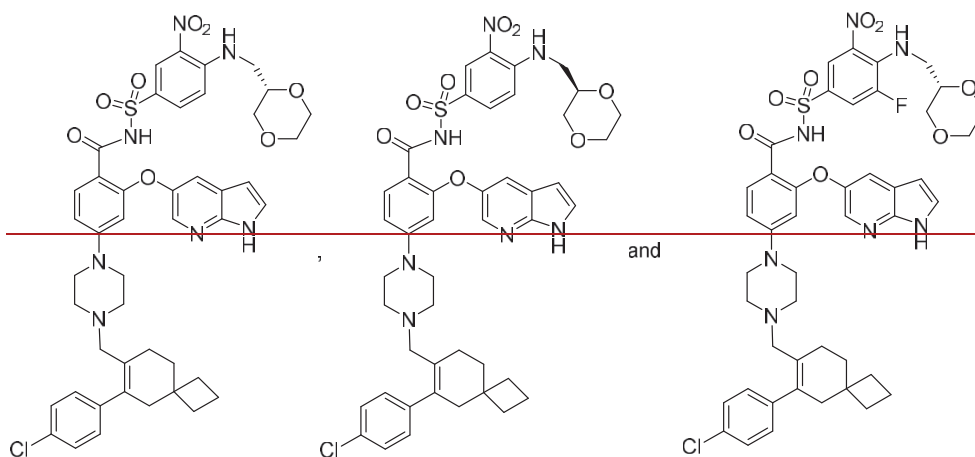
31. The compound of any one of claims 1, 2, 7, 9, or 19-28, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁵ is selected from the group consisting of:



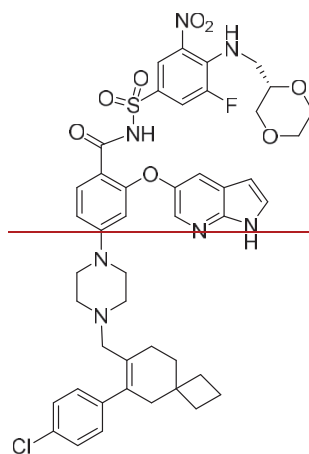
[illegible]

35. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, selected from one or more of the compounds of Table 1-C.

- 119 -



~~37. The compound of claim 36, or a pharmaceutically acceptable salt or solvate thereof, which is:~~



~~3836.~~ A pharmaceutical composition comprising the compound of any one of claims 1-~~3735~~, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

~~3937. Use of A method of treating a patient, the method comprising administering to the patient a therapeutically effective amount of~~ the compound of any one of claims 1-~~3735~~, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating wherein the patient has a hyperproliferative disease.

4038. The ~~method-use~~ of claim 3937, wherein the hyperproliferative disease is cancer.

4139. The ~~method-use~~ of claim 4038, wherein the cancer is selected from one or more of the cancers of Table 2.

4240. The ~~method-use~~ of claim 4038, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

4341. The ~~use method~~ of any one of claims 39-4237-40, ~~wherein further comprising administering a therapeutically effective amount of~~ a second therapeutic agent useful in the treatment of the disease is to be administered.

4442. ~~Use of the The~~ pharmaceutical composition of claim 38-36 in the manufacture of a medicament for treating for use in treating a hyperproliferative disease.

4543. The ~~use pharmaceutical composition~~ of claim 4442, wherein the hyperproliferative disease is cancer.

4644. The ~~use pharmaceutical composition~~ of claim 4543, wherein the cancer is selected from one or more of the cancers of Table 2.

4745. The ~~use pharmaceutical composition~~ of claim 4442, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

~~48. — A compound of any one of claims 1-37, or a pharmaceutically acceptable salt or solvate thereof, for use in treatment of a hyperproliferative disease.~~

~~49. — The compound of claim 48, wherein the hyperproliferative disease is cancer.~~

~~50. — The compound of claim 49, wherein the cancer is selected from one or more of the cancers of Table 2.~~

~~51. — The compound of claim 48, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.~~

~~52. — Use of a compound of any one of claims 1-37, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treatment of a hyperproliferative disease.~~

~~53. — The use of claim 52, wherein the hyperproliferative disease is cancer.~~

~~54. — The use of claim 53, wherein the cancer is selected from one or more of the cancers of Table 2.~~

~~55. — The use of claim 52, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.~~

5646. A kit comprising the compound of any one of claims 1-~~3735~~, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or solvate thereof, to a patient having a hyperproliferative disease.

5747. The kit of claim 5646, wherein the hyperproliferative disease is cancer.

5848. The kit of claim 5747, wherein the cancer is selected from one or more of the cancers of Table 2.

5949. The kit of claim 5747, 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, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

6050. The kit of any one of claims 5646-5949 further comprising one or more additional therapeutic agents.