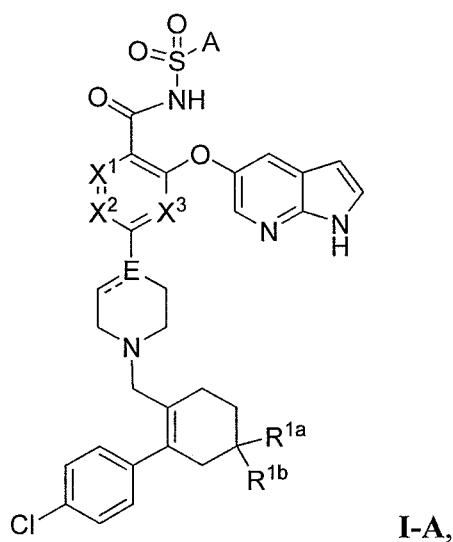


BRIEF SUMMARY

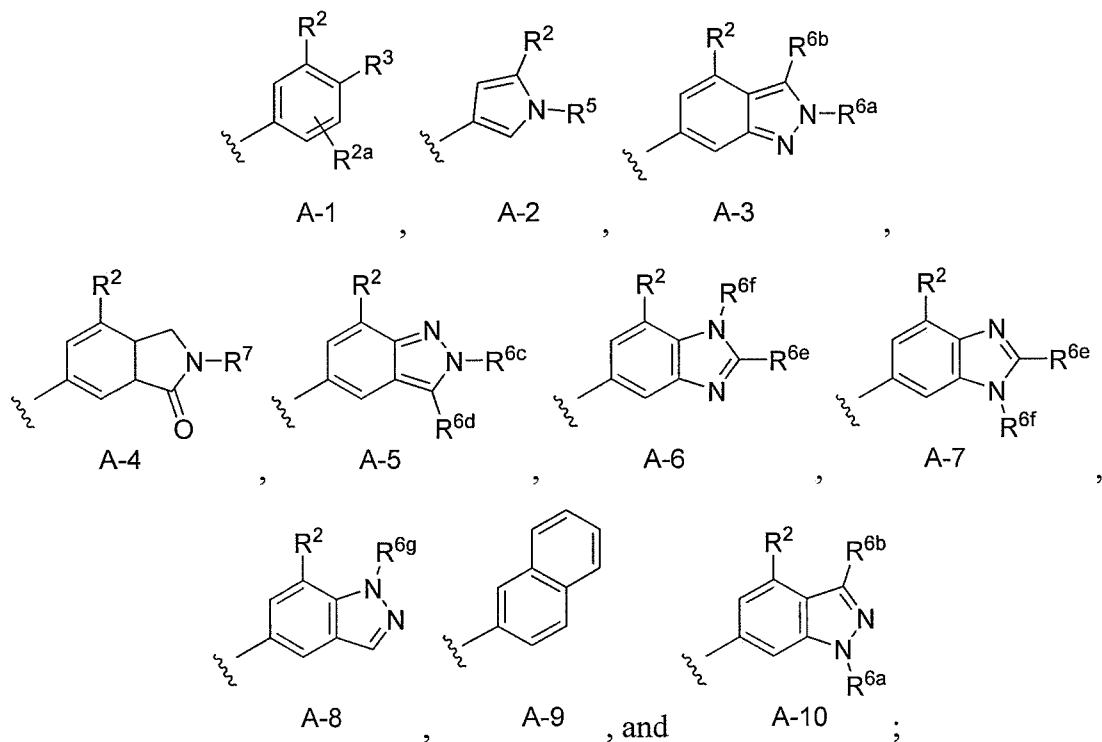
[0012] The present disclosure provides compounds represented by any one of Formulae I-A or I-VIII, below, and the pharmaceutically acceptable salts and solvates, e.g., hydrates, thereof, collectively referred to herein as "Compounds of the Disclosure."

[0012a] In another aspect, 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:



E is a carbon atom and $\equiv$ is a double bond; or

E is a -C(H)- and $\equiv$ is a single bond; or

E is a nitrogen atom and $\equiv$ is a single bond;

X^1 , X^2 , and X^3 are each independently selected from the group consisting of $-\text{CR}^8=$ and $-\text{N}=\text{}$;

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.

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

- [0013a] In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound as defined herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.
- [0014] 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] 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] 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] The present disclosure provides the use of Compounds of the Disclosure as inhibitors of Bcl-2.
- [0018] The present disclosure provides the use of Compounds of the Disclosure as inhibitors of Bcl-xL.
- [0019] 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.
- [0019a] In another aspect, the present disclosure provides a pharmaceutical composition as defined herein for use in treating a hyperproliferative disease.
- [0020] In another aspect, 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, 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] The present disclosure provides kit comprising a Compound of the Disclosure.
- [0022a] In another aspect, the present disclosure provides a kit comprising the compound as defined herein, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or solvate thereof, to a patient having a hyperproliferative disease.
- [0023] 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] 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 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.
- [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 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.

39. The pharmaceutical composition of claim 38 for use in treating a hyperproliferative disease.

40. The pharmaceutical composition of claim 39, wherein the hyperproliferative disease is cancer.

41. The pharmaceutical composition of claim 40, wherein the cancer is selected from one or more of the cancers of Table 2.

42. The pharmaceutical composition of claim 39, 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.

43. 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.

44. The compound of claim 43, wherein the hyperproliferative disease is cancer.

45. The compound of claim 44, wherein the cancer is selected from one or more of the cancers of Table 2.

46. The compound of claim 43, 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.

47. 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.

48. The use of claim 47, wherein the hyperproliferative disease is cancer.

49. The use of claim 48, wherein the cancer is selected from one or more of the cancers of Table 2.

50. The use of claim 47, 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.

51. A kit comprising the compound of any one of claims 1-37, 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.

52. The kit of claim 51, wherein the hyperproliferative disease is cancer.

53. The kit of claim 52, wherein the cancer is selected from one or more of the cancers of Table 2.

54. The kit 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 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.

55. The kit of any one of claims 51-54 further comprising one or more additional therapeutic agents.