INHIBITORS OF CYCLIN-DEPENDENT KINASE 7 (CDK7)

CROSS-REFERENCE TO RELATED APPLICATIONS

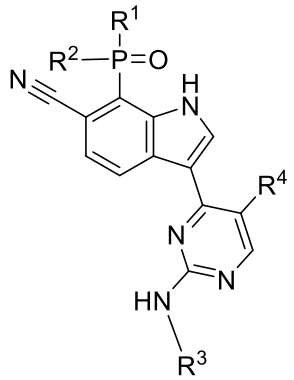
[1] This application claims the benefit of the filing date of U.S. provisional application No. 62/754,398, filed November 1, 2018; U.S. provisional application No. 62/877,189, filed July 22, 2019; U.S. provisional application No. 62/915,983, filed October 16, 2019, and U.S. provisional application No. 62/927,469, filed October 29, 2019. The content of each of these prior applications is hereby incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

[2] Members of the cyclin-dependent kinase (CDK) family are believed to play important roles in regulating cellular proliferation. The predominant target of the inhibitors described herein, CDK7, exists as a heterotrimeric complex in the cytosol and also forms the kinase core of the RNA polymerase (RNAP) II general transcription factor complex in the nucleus. Within that complex, CDK7 phosphorylates the C-terminal domain (CTD) of RNAP II, which is a requisite step in initiating gene transcription.

SUMMARY

[2a] In an aspect of the present disclosure, there is provided a compound of structural Formula (I):



(I),

or a pharmaceutically acceptable salt or isotopic form thereof, wherein:

R^1 is methyl or ethyl;

R^2 is methyl or ethyl;

R^3 is 5-methylpiperidin-3-yl, 5,5-dimethylpiperidin-3-yl, 6-methylpiperdin-3-yl, or 6,6-dimethylpiperidin-3-yl; and

R^4 is $-CF_3$ or chloro.

[2b] In another aspect of the present disclosure, there is provided an isotopic form of the

compound or the pharmaceutically acceptable salt thereof disclosed herein, wherein one or more hydrogen atoms in R^3 is replaced with deuterium.

[2c] In a further aspect of the present disclosure, there is provided a composition comprising a plurality of the compound or the pharmaceutically acceptable salt or isotopic form thereof disclosed herein, wherein the plurality constitutes an enantiomeric mixture of compounds having the R configuration at the 3-position of R^3 and compounds having the S configuration at the 3-position of R^3.

[2d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising (a) the compound or the pharmaceutically acceptable salt or isotopic form thereof disclosed herein, or the composition previously disclosed, and (b) a pharmaceutically acceptable carrier.

[2e] In a further aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a disease, wherein the disease is a proliferative disease, inflammatory disease, autoinflammatory disease, autoimmune disease, or infectious disease in a subject in need thereof.

[2f] In another aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a disease, wherein the disease is a proliferative disease in a subject who has been determined to have one or more of the following: a high grade cancer or a cancer in which CDK7 expression or activity is elevated; a cellular phenotype in which a steroid receptor is overexpressed in a biological sample of the disease cells; and resistance to a previously administered chemotherapeutic agent.

[2g] In a further aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a proliferative disease, wherein the pharmaceutical composition is to be administered in combination with an antimetabolite, a Bcl-2 inhibitor, a CDK4/6 inhibitor, a CDK9 inhibitor, a BET inhibitor, a Flt3 inhibitor, a MEK inhibitor, a PARP inhibitor, a PI3K inhibitor, an inhibitor of the PI3K/AKT/mTOR pathway, a platinum-based therapeutic agent, a SERM, a hormone receptor degrading agent, an aromatase inhibitor, or a taxane.

[2h] In another aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating triple-negative breast cancer, colorectal cancer, small cell lung cancer, or pancreatic cancer, wherein gemcitabine is to be further administered.

[2i] In a further aspect of the present disclosure, there is provided a kit comprising the pharmaceutical composition disclosed herein, instructions for use, and, optionally, a second agent

selected from an anti-proliferative agent, an anti-cancer agent, an immunosuppressant agent, and a pain relieving agent.

[2j] In another aspect of the present disclosure, there is provided a composition disclosed herein for use in treating a disease,

wherein the disease is a proliferative disease, inflammatory disease, autoinflammatory disease, autoimmune disease, or infectious disease; or

wherein the disease is a proliferative disease in a subject who has been determined to have one or more of the following: a high grade cancer or a cancer in which CDK7 expression or activity is elevated; a cellular phenotype in which a steroid receptor is overexpressed in a biological sample of the disease cells; and resistance to a previously administered chemotherapeutic agent; or

wherein the disease is a proliferative disease and wherein the proliferative disease is in a subject who has been determined to have one or more of the following: a high grade cancer or a cancer in which CDK7 expression or activity is elevated; a cellular phenotype in which a steroid receptor is overexpressed in a biological sample of the disease cells; and resistance to a previously administered chemotherapeutic agent; or

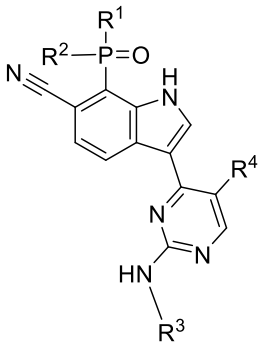
wherein the disease is a proliferative disease and wherein the pharmaceutical composition is to be administered in combination with an antimetabolite, a Bcl-2 inhibitor, a CDK4/6 inhibitor, a CDK9 inhibitor, a BET inhibitor, a Flt3 inhibitor, a MEK inhibitor, a PARP inhibitor, a PI3K inhibitor, an inhibitor of the PI3K/AKT/mTOR pathway, a platinum-based therapeutic agent, a SERM, a hormone receptor degrading agent, an aromatase inhibitor, or a taxane; or

for use in treating triple-negative breast cancer, colorectal cancer, small cell lung cancer, or pancreatic cancer, wherein gemcitabine is to be further administered.

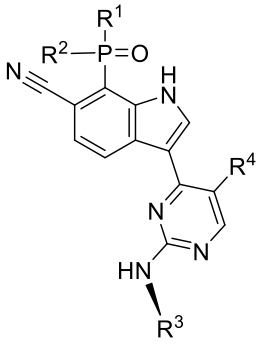
[3] The present disclosure provides selective CDK7 inhibitors that are chemical compounds having a formula disclosed herein (*e.g.*, Formula (I) or a subgenus (*e.g.*, Formula (Ia)) or species thereof) and, in various examples, pharmaceutically acceptable salts, solvates (*e.g.*, hydrates), stereoisomers or mixtures of stereoisomers (*e.g.*, racemic mixtures), tautomers, and isotopic forms (*e.g.*, deuterated forms) thereof, wherein various component parts of the compounds (*e.g.*, elements R^1, R^2, R^3, and R^4 of Formula (I) and subvariables thereof) are as described herein. Compounds of the present disclosure demonstrate surprising and unexpected superiority over other, comparator compounds in terms of selectivity for CDK7 over each of CDK2, CDK9 and CDK12; affinity for CDK7/cyclin H complexes; and anti-proliferative activity in cell line models, including a cell line model of triple-negative breast cancer. In addition, compounds of the present disclosure demonstrate good bioavailability in a rat model. Accordingly, in a first example, the present disclosure provides a

compound of Formula (I) or (Ia) or species thereof; in a second example, the present disclosure provides a salt thereof; in a third example, the present disclosure provides a solvate thereof; in a fourth example, the present disclosure provides a stereoisomer thereof of a mixture of stereoisomers (e.g., a racemic mixture); in a fifth example, the present disclosure provides a tautomer thereof; and in a sixth example, the present disclosure provides an isotopic form thereof. We may refer

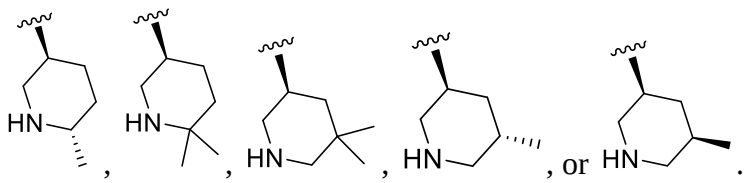
to these forms of a compound (*i.e.*, to the salt form, a solvate, stereoisomer, tautomer, or isotopic form) as "specified forms" of the compound. Also within the meaning of "specified form" are forms of a compound that manifest a combination of the attributes, features, or properties of a salt, solvate, stereoisomer, tautomer, or isotopic form. For example, the methods and uses of the present disclosure can be carried out with a salt that has been solvated (*e.g.*, a hydrated) or a salt of a stereoisomer, tautomer, or isotopic form of a compound of Formula I, I(a), or a species thereof; with a solvate (*e.g.*, hydrate) containing a salt, stereoisomer, tautomer, or isotopic form of a compound of Formula I, I(a), or a species thereof; with a stereoisomer of a compound of Formula I, or a species thereof, that is in the form of a salt or solvate (*e.g.*, hydrate) or is a tautomer or isotopic form of a compound of Formula I, or a species thereof; with a tautomer of a compound of Formula I, I(a), or a species thereof that is in the form of a salt or solvate (*e.g.*, hydrate) or that is a stereoisomer or isotopic form of a compound of Formula I, I(a), or a species thereof; or with an isotopic form of a compound of Formula I, I(a), or a species thereof that is a salt, solvate (*e.g.*, hydrate), stereoisomer, or tautomer of a compound of Formula I, I(a), or a species thereof. Any of these specified forms can be pharmaceutically acceptable and/or contained within a pharmaceutically acceptable composition (*e.g.*, formulated for oral administration). For example, a salt of a compound can be solvated; a stereoisomer can be solvated; a tautomer can be in a salt form and/or include isotopes; *etc*. Thus, the present disclosure encompasses, as a specified form, salts of the compound *per se* as well as salts of the stereoisomer, tautomeric, and isotopic forms of the compound. Similarly, and in case of doubt, either a given compound or a specified form thereof can be solvated or made as an isotopic form. For example, the present disclosure encompasses, as specified forms, solvates of the compound *per se* as well as solvates of a salt, stereoisomer, tautomer, or isotopic form thereof; the present disclosure encompasses isotopic forms of the compound *per se* as well as isotopic forms of the salt, solvate, stereoisomer, or tautomer thereof. These compositions (*e.g.*, salts of a compound, stereoisomer, tautomer, or isotopic form; solvates of a compound, a stereoisomer thereof, tautomer, or isotopic form; isotopic forms of a salt, solvate, stereoisomer, or isomeric form of a compound; and so forth) constitute compositions of the present disclosure useful as described herein. Accordingly, a pharmaceutical composition of the present disclosure, including any of those formulated as described further below (*e.g.*, for oral administration), can include a compound described herein or any one or more of the specified forms thereof. In one example, the present disclosure features a compound of structural Formula (I):



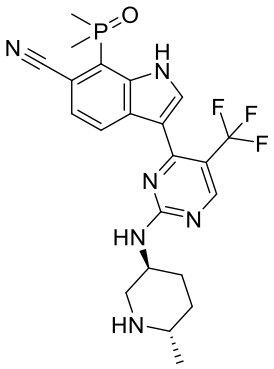
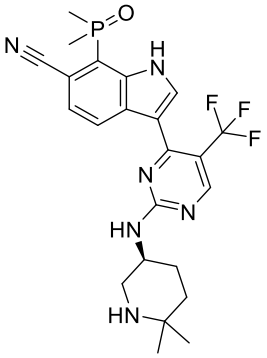
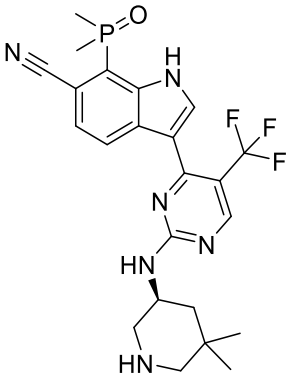
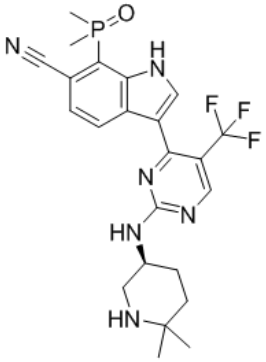
(I), or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, or isotopic form thereof, wherein R^1 is methyl or ethyl; R^2 is methyl or ethyl; R^3 is 5-methylpiperidin-3-yl, 5,5-dimethylpiperidin-3-yl, 6-methylpiperdin-3-yl, or 6,6-dimethylpiperidin-3-yl, wherein one or more hydrogen atoms in R^3 is optionally replaced by deuterium; and R^4 is $-CF_3$ or chloro. More specifically, in a compound of Formula (I) or in the pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or other specified form thereof (i) R^1 is methyl and R^2 is methyl or (ii) R^1 is methyl and R^2 is ethyl. In other examples, R^1 is ethyl and R^2 is ethyl. In some of these examples, R^4 is $-CF_3$. In other examples, R^4 is chloro. In some of the preceding examples, R^3 is 5-methylpiperidin-3-yl, R^3 is 5,5-dimethylpiperidin-3-yl, R^3 is 6-methyl-piperdin-3-yl, or R^3 is 6,6-dimethylpiperidin-3-yl, wherein one or more hydrogen atoms in R^3 is optionally replaced by deuterium. A compound of Formula (I) can have structural Formula (Ia):



(Ia), and the present disclosure encompasses pharmaceutically acceptable salts, solvates (*e.g.*, hydrates), tautomers, isotopic forms, or other specified forms of a compound of Formula (Ia), wherein R^3 is

[4]  . More specifically, in a compound of Formula (Ia) or a pharmaceutically acceptable salt, solvate, tautomer, isotopic form, or other specified form thereof (i) R^1 is methyl and R^2 is methyl or (ii) R^1 is methyl and R^2 is ethyl.

In other examples, R^1 is ethyl and R^2 is ethyl. In some examples, in a compound of Formula (Ia) or a specified form thereof, R^4 is $-CF_3$. In other examples, in a compound of Formula (Ia) or a specified form thereof, R^4 is chloro. In some examples, a compound of Formula (I) or (Ia) is:


,

, or

, and the present disclosure encompasses pharmaceutically acceptable salts, solvates (*e.g.*, hydrates), tautomers, isotopic forms or other specified forms of any one of the three foregoing compounds. In one example, the compound is

or a pharmaceutically acceptable salt thereof. The present disclosure also encompasses solvates (*e.g.*, hydrates), tautomers, isotopic forms or other specified forms of the foregoing compound. In isotopic forms, one or more hydrogen atoms in R^3 is replaced with deuterium. In other examples, none of the hydrogen atoms of a compound (*e.g.*, none of the hydrogen atoms in R^3) are replaced with deuterium. In other examples, the present disclosure features a solvate (*e.g.*, a hydrate) of a compound of Formula (I), (Ia), or a species thereof, with the elements R^1, R^2, R^3, and R^4 as described herein. In other examples, the present disclosure features a solvate (*e.g.*, a hydrate) of a salt of a compound of Formula (I), (Ia), or a species thereof; a solvate (*e.g.*, a hydrate) of a tautomer of a compound of Formula (I), (Ia), or a species thereof; and a solvate (*e.g.*, a hydrate) of an isomeric form of a compound of Formula (I), (Ia), or a species thereof. The solvate, in any of these examples, can be pharmaceutically acceptable and incorporated within a pharmaceutical composition, including any of those formulated as described below (*e.g.*, for oral administration).

[5] In another example, the present disclosure features a pharmaceutical composition, which we may also refer to as a pharmaceutical formulation, including a compound as described above (*i.e.*, a

compound of Formula (I), (Ia), a species thereof or a specified form thereof (*e.g.*, a pharmaceutically acceptable salt), and a pharmaceutically acceptable carrier. Pharmaceutical compositions of the present disclosure can be formulated for oral administration and/or formulated in unit dosage form (including, *e.g.*, a compound of Formula (I), (Ia), a species thereof, or a salt thereof).

[6] In another example, the present disclosure features methods or "use" of a pharmaceutical composition described herein in treating or preventing a disease, wherein the disease is a proliferative disease, inflammatory disease, autoinflammatory disease, autoimmune disease, or infectious disease (each encompassing the specific diseases described herein; *see, e.g.*, the definitions provided herein) in a subject in need thereof. Methods of treatment may include a step of administering a pharmaceutical composition and "use" of the present compositions may be in the preparation of a medicament. In one example, the disease is a proliferative disease (*e.g.*, a cancer, benign neoplasm, or pathologic angiogenesis). For example, the cancer can be a blood cancer (*e.g.*, a leukemia (*e.g.*, AML) or lymphoma). In other examples, the cancer is characterized by the presence of a solid tumor (in, *e.g.*, the breast (*e.g.*, a TNBC, HR+, or other type of breast cancer described herein), GI tract (*e.g.*, a CRC), lung (*e.g.*, NSCLC or other type of lung cancer described herein), pancreas, or prostate). In other examples, the cancer is a fallopian tube cancer; an ovarian cancer (*e.g.*, a high grade serous ovarian cancer, epithelial ovarian cancer, or clear cell ovarian cancer); a cancer of the central nervous system (*e.g.*, a glioma); a melanoma. or Ewing's sarcoma. In other examples, the cancer is a pancreatic cancer; a primary peritoneal cancer; prostate cancer; retinoblastoma; or a squamous cell cancer of the head or neck. In one example, the various methods and uses described herein (*e.g.*, in treating or preventing a proliferative disease, including but not limited to those just described, an inflammatory disease, autoinflammatory disease, autoimmune disease, or infectious disease) are applied to a subject who has been determined to have one or more of the following (as determined in, for example, a biological sample of disease cells obtained from the subject): a high grade cancer (*e.g.*, high grade serous ovarian cancer (HGSOC) or breast cancer); a cellular phenotype in which a steroid receptor is present and/or overexpressed or otherwise abberent; a triple-negative breast cancer; and/or resistance to a previously administered chemotherapeutic agent (*e.g.*, a Bcl-2 inhibitor such as venetoclax, a BET inhibitor, a CDK4/6 inhibitor such as palbociclib or ribociclib, a CDK9 inhibitor such as alvocidib, a FLT3 inhibitor, a MEK inhibitor such as trametinib, cobimetinib, or binemetinib (useful in combination with a compound of Formula (I), (Ia), a species thereof or specified form thereof in treating melanoma), a PARP inhibitor, such as olaparib or niraparib, a PI3K inhibitor, such as alpelisib, apitolisib (GDC-0980), idelalisib, copanlisib, duvelisib, pictilisib, or capecitabine (useful in combination with a compound of Formula (I), (Ia), a species thereof or

specified form thereof in treating, *e.g.*, HR+ breast cancer, TNBC, lymphoma (*e.g.*, follicular lymphoma or non-Hodgkin lymphoma), or leukemia (*e.g.*, CLL), an inhibitor of the PI3K/AKT/mTOR pathway (*e.g.*, gedatolisib), a platinum-based therapeutic agent such as cisplatin, oxaliplatin, nedaplatin, carboplatin, phenanthriplatin, picoplatin, satraplatin (JM216), or triplatin tetranitrate (useful in combination with a compound of Formula (I), (Ia), a species thereof or specified form thereof in treating, *e.g.*, a lung cancer such as SCLC or a GI tract cancer such as CRC), a SERM, such as tamoxifen, raloxifene, or toremifene, a steroid receptor degrading agent (*e.g.*, a SERD, such as fulvestrant), or an agent that inhibits the production of estrogen (*e.g.*, an aromatase inhibitor such as anastrozole (available as Arimidex®), exemestane (available as Aromasin®), and letrozole (available as Femara®). Combination therapies including one or more of these agents (*e.g.*, for a total of two or three administered agents) are also within the scope of the present disclosure and are discussed further herein. For example, in one example, the methods encompass the use of or administration of a compound of Formula (I), (Ia), a species thereof or a specified form thereof, in combination with a SERD, such as fulvestrant, or an aromatase inhibitor such as letrozole, to treat a cancer (*e.g.*, a breast cancer (*e.g.*, an HR+/ER+ breast cancer)) resistant to treatment with a CDK4/6 inhibitor such as palbociclib or ribociclib. In one example, the methods encompass the use of or administration of a compound of Formula (I), (Ia), a species thereof or a specified form thereof, in combination with a MEK inhibitor, such as trametinib, which can be used in further combination with dabrafenib, vemurafenib, or encorafenib.

[7] In another example, the present disclosure features kits comprising a pharmaceutical composition or formulation described herein and instructions for use, and, optionally, a "second" agent selected from an anti-proliferative agent, an anti-cancer agent, an immunosuppressant agent, and a pain-relieving agent, including any one or more of those specifically disclosed below). The kits can comprise a container with a compound described herein or a specified form thereof (*e.g.*, a pharmaceutically acceptable salt, solvate, stereoisomer, tautomer, or isotopic form thereof), or a composition (*e.g.*, a pharmaceutically acceptable composition or formulation, as described herein) comprising the compound, salt, solvate, stereoisomer, tautomer or isotopic form thereof. In any example of the kit, instructions for use can be included, and that use can be in treating a disease described herein (*e.g.*, a blood cancer, a cancer characterized by the presence of a solid tumor (in, *e.g.*, the breast, GI tract (*e.g.*, a CRC), lung (*e.g.*, NSCLC), pancreas, or prostate), or Ewing's sarcoma.

[8] The pharmaceutically acceptable compositions of the present disclosure include a composition disclosed herein (*e.g.*, a compound described herein or a specified form thereof (*e.g.*, a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, tautomer, or isotopic form

thereof (or another specified form, such as a solvate of a salt of a compound of Formula (I))) and a pharmaceutically acceptable carrier. In certain examples, the pharmaceutical compositions include a therapeutically or prophylactically effective amount of a compound of Formula (I) or a subgenus (*e.g.*, Formula (Ia)) or species thereof, or a specified form thereof (*e.g.*, a pharmaceutically acceptable salt, solvate, stereoisomer, tautomer, isotopic form, or other specified form thereof). The pharmaceutical composition may be useful in treating and/or preventing a proliferative or infectious disease, as described further 0below. The present disclosure also provides methods of making and using the compounds and other compositions described herein (*e.g.*, any one of the specified forms or pharmaceutical compositions containing a compound of the present disclosure or a specified form thereof) as therapeutics for the prevention and/or treatment of diseases associated with overexpression and/or aberrant activity of CDK7. Amenable diseases include proliferative diseases (*e.g.*, cancers (*e.g.*, a breast cancer, a leukemia or other blood cancer, melanoma, multiple myeloma (MM), ovarian cancer, a cancer of the GI tract (*e.g.*, a CRC) or lung (*e.g.*, NSCLC), pancreatic cancer, prostate cancer, or Ewing's sarcoma), benign neoplasms, and pathologic angiogenesis), inflammatory diseases, autoinflammatory diseases, autoimmune diseases, and infectious diseases, as described herein (*see*, *e.g.*, the definitions).

BRIEF DESCRIPTION OF THE DRAWINGS

[9] FIG. 1 is a table depicting the inhibitory and dissociation constants and selectivity of the indicated compounds (three compounds of the invention and four comparators) against CDK2, CDK7, CDK9, and CDK12.

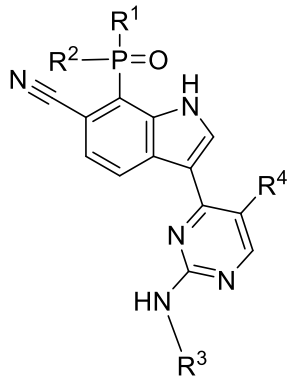
[10] FIG. 2 is a line graph depicting changes in tumor volume (mm^3) over time (days) in the palbociclib-resistant HR+BC PDX model ST1799 (as described further in the Examples below).

[11] FIG. 3 is a line graph depicting changes in tumor volume (mm^3) over time (days) in the palbociclib- and fulvestrant-resistant HR+BC PDX model ST941 (as described further in the Examples below).

[12] FIG. 4 is a panel showing three line graphs that depict changes in tumor volume (mm^3) over time (days) in PDX models of TNBC (BR5010; top), small cell lung cancer (LU5178; middle), and ovarian cancer (OV15398; bottom). The animals were treated with Compound 101 as described in Example 10. Data obtained from vehicle-treated (control) animals is represented by filled circles (upper traces in each graph). Data from animals modeling TNBC and given 10 mg/kg Compound 101 QD are represented in the top graph by filled squares; the dose of 5 mg/kg BID is represented by triangles. Triangles also represent data obtained from the animal models of SCLC and ovarian cancer treated with Compound 101 in the middle and bottom graphs.

What is claimed is:

1. A compound of structural Formula (I):



(I),

or a pharmaceutically acceptable salt or isotopic form thereof, wherein:

R^1 is methyl or ethyl;

R^2 is methyl or ethyl;

R^3 is 5-methylpiperidin-3-yl, 5,5-dimethylpiperidin-3-yl, 6-methylpiperdin-3-yl, or 6,6-dimethylpiperidin-3-yl; and

R^4 is $-CF_3$ or chloro.

2. The compound of claim 1 or the pharmaceutically acceptable salt or isotopic form thereof, wherein (i) R^1 is methyl and R^2 is methyl or (ii) R^1 is methyl and R^2 is ethyl.

3. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^4 is $-CF_3$.

4. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^4 is chloro.

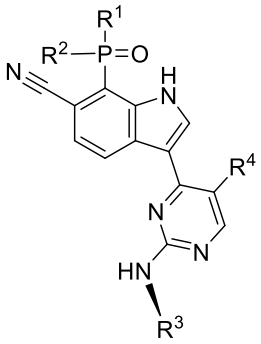
5. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^3 is 5-methylpiperidin-3-yl.

6. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^3 is 5,5-dimethylpiperidin-3-yl.

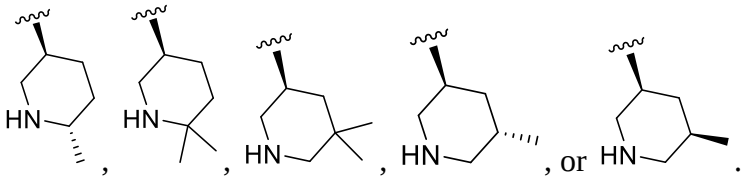
7. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^3 is 6-methylpiperdin-3-yl.

8. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^3 is 6,6-dimethylpiperidin-3-yl.

9. The compound of claim 1, having structural Formula (Ia):



(Ia), or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^3 is



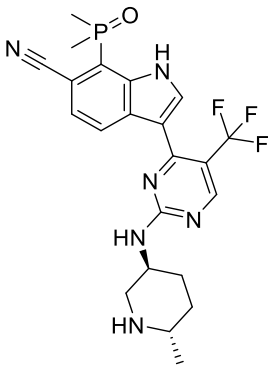
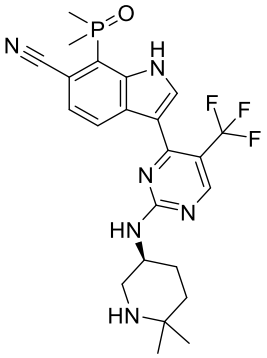
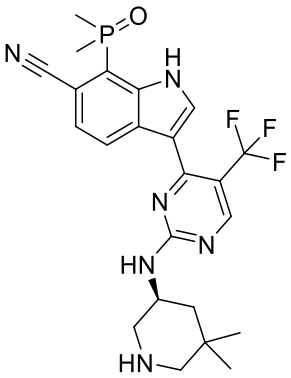
, , , , or .

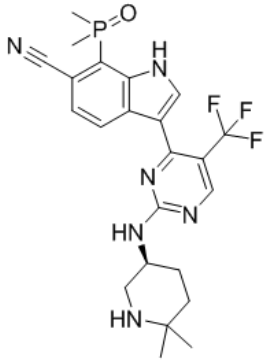
10. The compound of claim 9 or the pharmaceutically acceptable salt or isotopic form thereof, wherein (i) R^1 is methyl and R^2 is methyl or (ii) R^1 is methyl and R^2 is ethyl.

11. The compound of claim 9 or claim 10 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^4 is $-CF_3$.

12. The compound of claim 9 or claim 10 or the pharmaceutically acceptable salt or isotopic form thereof, wherein R^4 is chloro.

13. The compound of claim 9, wherein the compound is:


,

, or

, or is a pharmaceutically acceptable salt or isotopic form of any one of the foregoing compounds.

14. The compound of claim 13, wherein the compound is

, or a pharmaceutically acceptable salt thereof.

15. An isotopic form of the compound of claim 1, claim 9, or claim 13, or the pharmaceutically acceptable salt thereof, wherein one or more hydrogen atoms in R^3 is replaced with deuterium.

16. The compound of claim 1, claim 9, or claim 13, or the pharmaceutically acceptable salt thereof, wherein none of the atoms are replaced with an isotope thereof.

17. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt or isotopic form thereof has the S configuration at the 3-position of R^3.

18. The compound of claim 1, wherein the compound or the pharmaceutically acceptable salt or isotopic form thereof has the R configuration at the 3-position of R^3.

19. A composition comprising a plurality of the compound of claim 1 or the pharmaceutically acceptable salt or isotopic form thereof, wherein the plurality constitutes an

enantiomeric mixture of compounds having the R configuration at the 3-position of R^3 and compounds having the S configuration at the 3-position of R^3.

20. The composition of claim 19, wherein the enantiomeric mixture is a racemic mixture.

21. A pharmaceutical composition comprising (a) the compound of any one of claims 1, 9, 13, 14, 17, or 18, or the pharmaceutically acceptable salt or isotopic form thereof, or the composition of claim 19 or claim 20, and (b) a pharmaceutically acceptable carrier.

22. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition is formulated for oral administration.

23. The pharmaceutical composition of claim 21, wherein the composition is formulated in unit dosage form.

24. Use of the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating a disease, wherein the disease is a proliferative disease, inflammatory disease, autoinflammatory disease, autoimmune disease, or infectious disease in a subject in need thereof.

25. Use of the pharmaceutical composition of claim 24, wherein the disease is a proliferative disease.

26. Use of the pharmaceutical composition of claim 25, wherein the proliferative disease is a cancer, benign neoplasm, or pathologic angiogenesis.

27. Use of the pharmaceutical composition of claim 26, wherein the cancer is a blood cancer.

28. Use of the pharmaceutical composition of claim 26, wherein the cancer is characterized by the presence of a solid tumor.

29. Use of the pharmaceutical composition of claim 28, wherein the cancer is a breast cancer, a gastrointestinal (GI) tract cancer, a lung cancer, a pancreatic cancer, a prostate cancer, an ovarian cancer, or an osteosarcoma.

30. Use of the pharmaceutical composition of claim 29, wherein the breast cancer is a hormone receptor-positive (HR+) breast cancer, optionally an estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) breast cancer, a hormone receptor-negative cancer, a triple negative breast cancer (TNBC; ER-/PR-/HER2-), or a triple-positive breast cancer.

31. Use of the pharmaceutical composition of claim 29, wherein the GI tract cancer is colorectal cancer, the lung cancer is small cell lung cancer or non-small cell lung cancer, the pancreatic cancer is pancreatic ductal adenocarcinoma, and the osteosarcoma is Ewing's sarcoma.

32. Use of the pharmaceutical composition of claim 27, wherein the blood cancer is multiple myeloma or myelodysplastic syndrome (MDS).

33. Use of the pharmaceutical composition of claim 27, wherein the blood cancer is a leukemia.

34. Use of the pharmaceutical composition of claim 33, wherein the leukemia is acute lymphocytic leukemia (ALL) acute myelocytic leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), chronic neutrophilic leukemia (CNL), or chronic myelomonocytic leukemia (CMML).

35. Use of the pharmaceutical composition of claim 27, wherein the blood cancer is a lymphoma.

36. Use of the pharmaceutical composition of claim 35, wherein the lymphoma is Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), or a diffuse large cell lymphoma (DLCL).

37. Use of the pharmaceutical composition of claim 36, wherein the DLCL is diffuse large B cell lymphoma (DLBCL).

38. Use of the pharmaceutical composition of claim 35, wherein the lymphoma is mantle cell lymphoma (MCL) or a marginal zone lymphoma (MZL).

39. Use of the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating a disease, wherein the disease is a proliferative disease in a subject who

has been determined to have one or more of the following: a high grade cancer or a cancer in which CDK7 expression or activity is elevated; a cellular phenotype in which a steroid receptor is overexpressed in a biological sample of the disease cells; and resistance to a previously administered chemotherapeutic agent.

40. Use of the pharmaceutical composition of claim 39, wherein the previously administered chemotherapeutic agent is a Bcl-2 inhibitor, CDK4/6 inhibitor, a BET inhibitor, a Flt3 inhibitor, a MEK inhibitor, a PARP inhibitor, a PI3K inhibitor, an inhibitor of the PI3K/AKT/mTOR pathway, a platinum-based therapeutic agent, a SERM, a steroid receptor degrading agent, or an aromatase inhibitor.

41. Use of the pharmaceutical composition of claim 40, wherein the Bcl-2 inhibitor is venetoclax, the CDK4/6 inhibitor is Palbociclib or ribociclib, the MEK inhibitor is trametinib, the PARP inhibitor is Olaparib, the PI3K inhibitor is alpelisib, the platinum-based therapeutic agent is cisplatin, oxaliplatin, nedaplatin, carboplatin, phenanthriplatin, picoplatin, satraplatin, or triplatin tetranitrate, the SERM is tamoxifen, the steroid receptor degrading agent is fulvestrant, and the aromatase inhibitor is anastrozole, exemestane, or letrozole.

42. Use of the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating a proliferative disease, wherein the pharmaceutical composition is to be administered in combination with an antimetabolite, a Bcl-2 inhibitor, a CDK4/6 inhibitor, a CDK9 inhibitor, a BET inhibitor, a Flt3 inhibitor, a MEK inhibitor, a PARP inhibitor, a PI3K inhibitor, an inhibitor of the PI3K/AKT/mTOR pathway, a platinum-based therapeutic agent, a SERM, a hormone receptor degrading agent, an aromatase inhibitor, or a taxane.

43. Use of the pharmaceutical composition of claim 42, wherein the Bcl-2 inhibitor is venetoclax, the CDK4/6 inhibitor is palbociclib or ribociclib, the CDK9 inhibitor is alvocidib, seliciclib, or voruciclib, the Flt3 inhibitor is crenolanib, gilteritinib, lestautinib, ponatinib, sorafenib, sunitinib, pacritinib, pexidartinib, quizartinib, or midostaurin, the MEK inhibitor is trametinib, the PARP inhibitor is olaparib, rucaparib, talazoparib, veliparib, or niraparib, the PI3K inhibitor is alpelisib, the platinum-based therapeutic agent is cisplatin, oxaliplatin, nedaplatin, carboplatin, phenanthriplatin, picoplatin, satraplatin, or triplatin tetranitrate, the SERM is tamoxifen, the hormone receptor degrading agent is fulvestrant, the aromatase inhibitor is exemestane or anastrasole, and the taxane is docetaxel, paclitaxel, or paclitaxel protein-bound.

44. Use of the pharmaceutical composition of claim 43, wherein (a) venetoclax is to be administered and the proliferative disease is chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), or (b) venetoclax and azacitidine, decitabine, or low-dose cytarabine is to be administered and the proliferative disease is acute myelocytic leukemia (AML) in patients who are at least 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy.

45. Use of the pharmaceutical composition of claim 42, wherein the antimetabolite is 5-fluorouracil (5-FU).

46. Use of the pharmaceutical composition of claim 42, wherein leucovorin, methotrexate, or oxaliplatin is to be further administered.

47. Use of the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating triple-negative breast cancer, colorectal cancer, small cell lung cancer, or pancreatic cancer, wherein gemcitabine is to be further administered.

48. A kit comprising the pharmaceutical composition of claim 21, instructions for use, and, optionally, a second agent selected from an anti-proliferative agent, an anti-cancer agent, an immunosuppressant agent, and a pain relieving agent.

49. A pharmaceutical composition of claim 21 for use in treating a disease,
wherein the disease is a proliferative disease, inflammatory disease, autoinflammatory disease, autoimmune disease, or infectious disease; or
wherein the disease is a proliferative disease in a subject who has been determined to have one or more of the following: a high grade cancer or a cancer in which CDK7 expression or activity is elevated; a cellular phenotype in which a steroid receptor is overexpressed in a biological sample of the disease cells; and resistance to a previously administered chemotherapeutic agent; or
wherein the disease is a proliferative disease and wherein the proliferative disease is in a subject who has been determined to have one or more of the following: a high grade cancer or a cancer in which CDK7 expression or activity is elevated; a cellular phenotype in which a steroid receptor is overexpressed in a biological sample of the disease cells; and resistance to a previously administered chemotherapeutic agent; or
wherein the disease is a proliferative disease and wherein the pharmaceutical composition is to be administered in combination with an antimetabolite, a Bcl-2 inhibitor, a CDK4/6 inhibitor, a

CDK9 inhibitor, a BET inhibitor, a Flt3 inhibitor, a MEK inhibitor, a PARP inhibitor, a PI3K inhibitor, an inhibitor of the PI3K/AKT/mTOR pathway, a platinum-based therapeutic agent, a SERM, a hormone receptor degrading agent, an aromatase inhibitor, or a taxane; or

for use in treating triple-negative breast cancer, colorectal cancer, small cell lung cancer, or pancreatic cancer, wherein gemcitabine is to be further administered.