INHIBITORS OF CYCLIN-DEPENDENT KINASE 7 (CDK7)

CROSS-REFERENCE TO RELATED APPLICATIONS

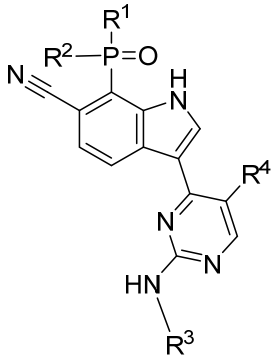
[1] This application claims the benefit of the filing date of U.S. provisional application No. 62/754,398, filed November 1, 2018; U.S. provisional application No. 62/877,189, filed July 22, 2019; U.S. provisional application No. 62/915,983, filed October 16, 2019, and U.S. provisional application No. 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 thereof, wherein:

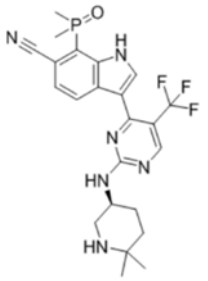
R^1 is methyl or ethyl;

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 the compound



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[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 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 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

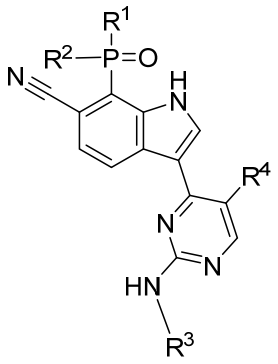
for use in treating triple-negative breast cancer, colorectal cancer, small cell lung cancer, or pancreatic cancer, wherein gemcitabine is to be further administered.

[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

What is claimed is:

1. A compound of structural Formula (I):



(I),

or a pharmaceutically acceptable salt 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 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 thereof, wherein R^4 is $-CF_3$.

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

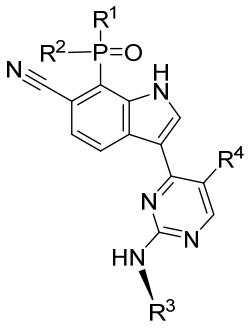
5. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt thereof, wherein R^3 is 5-methylpiperidin-3-yl.

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

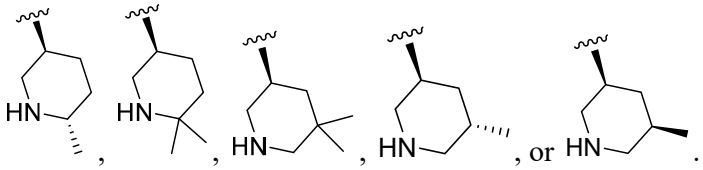
7. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt thereof, wherein R^3 is 6-methylpiperdin-3-yl.

8. The compound of claim 1 or claim 2 or the pharmaceutically acceptable salt 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 thereof, wherein R^3 is



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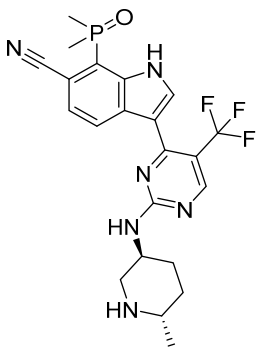
10. The compound of claim 9 or the pharmaceutically acceptable salt thereof, wherein (i) R^1 is methyl and R^2 is methyl or (ii) R^1 is methyl and R^2 is ethyl.

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

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

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



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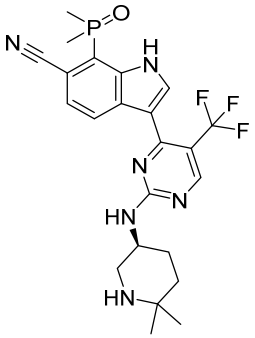
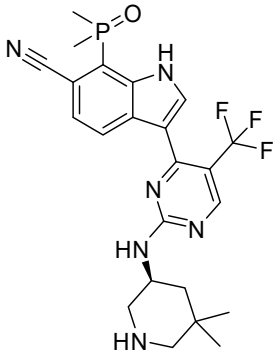
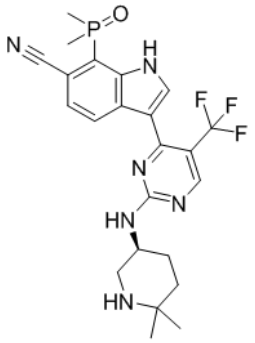
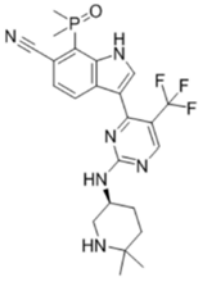


, or


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

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


, or a pharmaceutically acceptable salt thereof.

15. The compound


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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 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 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 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 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 42, wherein the antimetabolite is 5-fluorouracil (5-FU).

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

46. 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.

47. 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.

48. 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.