

COMPOUNDS USEFUL FOR INHIBITING CDK7

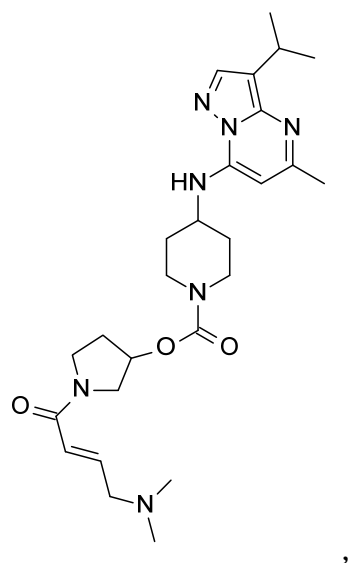
The present invention relates to compounds useful for inhibiting cyclin-dependent kinase 7 (CDK7), pharmaceutical compositions, and methods for treating diseases related to CDK7 activity.

Cyclin-dependent kinases (CDKs) are a major class of kinases and are important in cancer cell proliferation and deregulated oncogenic transcription. CDK7 binds to cyclin H and MAT1 to form a trimeric cyclin-activating kinase (CAK) that performs its function by phosphorylating other CDKs involved in cell-cycle control. These complexes control specific transitions between two subsequent phases in the cell cycle. CDK7 is implicated in both temporal control of the cell cycle and transcriptional activity. CDK7 is implicated in the transcriptional initiation process by phosphorylation of Rbp1 subunit of RNA Polymerase II (RNAPII). Uncontrolled cell proliferation and deregulated transcription is a cancer hallmark. Targeting CDK7 selectively may offer an advantage by simultaneously inhibiting active transcription and cell-cycle progression. Therefore, CDK7 is a promising target for the treatment of cancer, in particular aggressive and hard-to-treat cancers.

Small molecule inhibitors against CDK7 have been reported in the literature (*see, e.g.*, WO 2015/154022, WO 2016/142855, WO 2016/160617, WO 2016/193939, and WO 2017/044858). There remains a need to provide CDK7 inhibitors which can be used in the treatment of cell proliferative disorders, such as cancer. Additionally, there is a need to provide CDK7 inhibitors which are selective for CDK7 compared to other CDKs.

Summary

In one aspect, the present disclosure refers to a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

In a further aspect, the present disclosure refers to a compound or salt thereof disclosed herein, for use in therapy.

In another aspect, the present disclosure refers to a compound or salt thereof disclosed herein, for use in the treatment of urothelial cancer, uterine cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, cervical cancers, prostate cancer, haematological cancers, sarcomas, skin cancers, or gliomas.

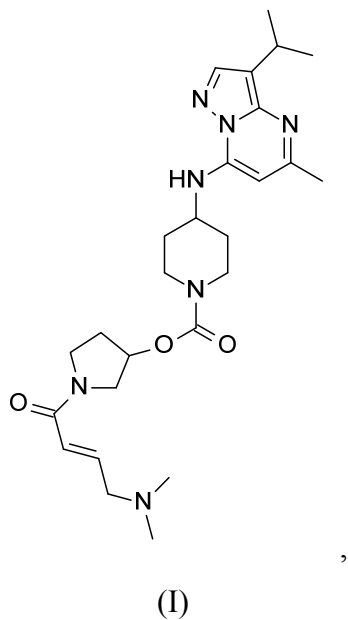
In a further aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a urothelial cancer, uterine cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, cervical cancers, prostate cancer, haematological cancers, sarcomas, skin cancers, or gliomas.

Description

The present invention provides novel compounds that are selective CDK7 inhibitors. Such new compounds could address the need for potent, effective treatment of cancer, especially cancer with deregulated transcription. The present invention could also address the need for potent, effective treatment of urothelial cancer, uterine cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, cervical cancers, prostate cancer, haematological cancers, sarcomas, skin cancers, and/or gliomas.

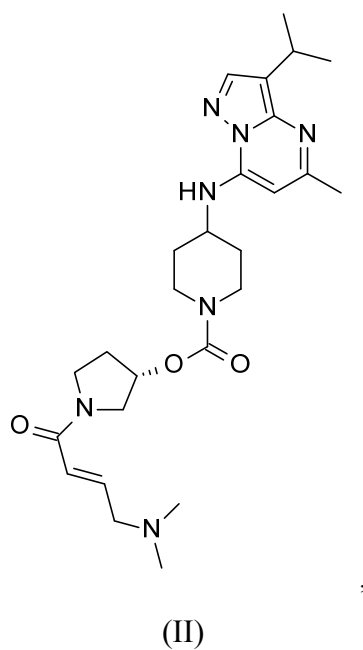
What is Claimed is:

1. A compound of formula (I)



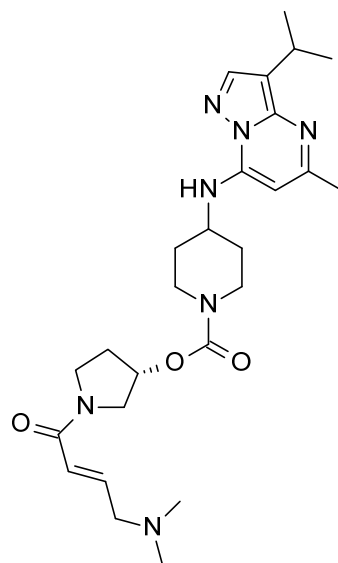
- 5 or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 of formula (II)



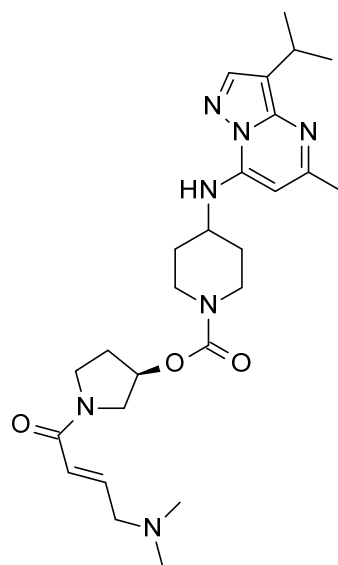
- 10 or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 2 of formula (II)



(II)

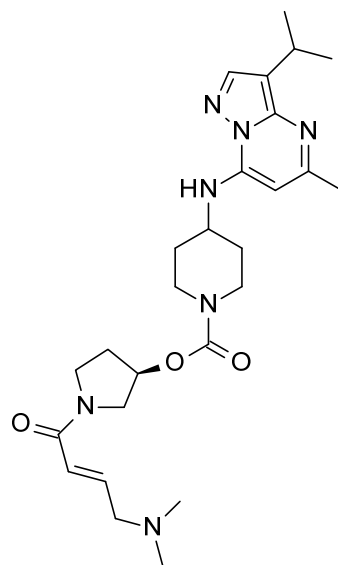
4. The compound according to Claim 1 of formula (III)



(III)

or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 4 of formula (III)



(III)

6. The compound or salt thereof according to Claim 2 which is a chloride, besylate,
5 or hemi-edisylate salt.
7. The compound or salt thereof according to Claim 4 which is a chloride, besylate,
or hemi-edisylate salt.

8. The compound or salt thereof according to Claim 2 in a crystalline salt form.
9. The compound or salt thereof according to Claim 8 which is crystalline [(3S)-1-
[(E)-4-(dimethylamino)but-2-enoyl]pyrrolidin-3-yl] 4-[(3-isopropyl-5-methyl-
5 pyrazolo[1,5-a]pyrimidin-7-yl)amino]piperidine-1-carboxylate besylate
characterized by a X-ray powder diffraction pattern having characteristic peaks
using CuK α radiation, in $2\theta \pm 0.2^\circ$, occurring at 21.5° in combination with one or
more peaks selected from the group consisting of 12.4° , 17.3° , and 15.8° .
- 10 10. The compound or salt thereof according to Claim 8 which is [(3S)-1-[(E)-4-
(dimethylamino)but-2-enoyl]pyrrolidin-3-yl] 4-[(3-isopropyl-5-methyl-
pyrazolo[1,5-a]pyrimidin-7-yl)amino]piperidine-1-carboxylate hemi-edisylate
hydrate characterized by a X-ray powder diffraction pattern having characteristic
peaks using CuK α radiation, in $2\theta \pm 0.2^\circ$, occurring at 18.5° in combination with
15 one or more peaks selected from the group consisting of 21.5° , 16.7° , and 15.2° .

11. A pharmaceutical composition comprising a compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.
- 5 12. The pharmaceutical composition according to Claim 11 comprising one or more other therapeutic agents.

13. A compound or salt thereof according to any one of Claims 1 to 10, for use in therapy.

5 14. A compound or salt thereof, according to any one of Claims 1 to 10, for use in the treatment of urothelial cancer, uterine cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, cervical cancers, prostate cancer, haematological cancers, sarcomas, skin cancers, or gliomas.

10 15. The compound or salt thereof for use according to Claim 14 wherein the cancer is colorectal cancer, breast cancer, lung cancer, ovarian cancer, or gastric cancer.

16. The compound or salt thereof for use according to either Claim 14 or 15 wherein the cancer is breast cancer.

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17. The compound or salt thereof for use according to any one of Claims 13 to 16,
also comprising performing an *in vitro* assay using a biological sample from the
patient, determining the presence of at least one inactivating mutation in the
ARID1A, *KMT2C*, *KMT2D* and *RB1* genes, and wherein a therapeutically
5 effective amount of the compound or salt thereof is to be administered to the
patient if at least one inactivating mutation in any of genes is present.
18. The compound or salt thereof for use according to Claim 17 wherein the
biological sample is a tumor sample and the sample is assayed by genomic/DNA
10 sequencing.
19. The compound or salt thereof for use according to either Claim 17 or 18 wherein
the sample is to be obtained from the patient prior to the first administration of the
compound or the salt thereof to the patient.
- 15 20. The compound for salt thereof for use according to any one of Claims 13 to 19
wherein a patient is selected for treatment by having at least one inactivating
mutation in the *ARID1A* gene.
- 20 21. The compound or salt thereof for use according to any one of Claims 13 to 19
wherein a patient is selected for treatment by having at least one inactivating
mutation in the *KMT2C* gene.
- 25 22. The compound or salt thereof for use according to any one of Claims 13 to 19
wherein a patient is selected for treatment by having at least one inactivating
mutation in the *KMT2D* gene.
- 30 23. The compound or salt thereof for use according to any one of Claims 13 to 19
wherein a patient is selected for treatment by having at least one inactivating
mutation in the *RB1* gene.
24. The compound or salt thereof for use according to any one of Clams 13 to 23
wherein the compound of salt thereof is to be administered to the patient at a dose
of about 1 mg to 2 g.

25. A use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a urothelial cancer, uterine cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, cervical cancers, prostate cancer, haematological cancers, sarcomas, skin cancers, or gliomas.
26. The use according to Claim 25 wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, lung cancer, ovarian cancer, or gastric cancer.
27. The use according to either Claim 25 or 26, also comprising performing an *in vitro* assay using a biological sample from the patient, determining the presence of at least one inactivating mutation in the *ARID1A*, *KMT2C*, *KMT2D* and *RB1* genes, and wherein a therapeutically effective amount of the compound or salt thereof is to be administered to the patient if at least one inactivating mutation in any of the genes is present.
28. The use according to Claim 27 wherein the biological sample is a tumor sample and the sample is assayed by genomic/DNA sequencing.
29. The use according to any one of Claims 25 to 28 wherein the sample is to be obtained from the patient prior to the first administration of the compound or the salt thereof to the patient.
30. The use according to any one of Claims 25 to 29 wherein a patient is selected for having at least one inactivating mutation in the *ARID1A* gene.
31. The use according to any one of Claims 25 to 29 wherein a patient is selected for having at least one inactivating mutation in the *KMT2C* gene.
32. The use according to any one of Claims 25 to 29 wherein a patient is selected for having at least one inactivating mutation in the *KMT2D* gene.

33. The use according to any one of Claims 25 to 29 wherein a patient is selected for having at least one inactivating mutation in the *RB1* gene.
- 5 34. The use according to any one of Claims 25 to 29 wherein the compound of salt thereof is to be administered to the patient at a dose of about 1 mg to 2 g.