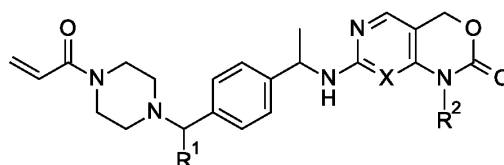


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WE CLAIM:

1. A method of treating cancer, comprising administering to a human cancer subject having an IDH1 R132 mutation and one or more secondary IDH1 mutations a therapeutically effective amount of a compound of the formula:



wherein:

R¹ is -CH₂CH(CH₃)₂, -CH₂CH₃, -CH₂CH₂OCH₃, or -CH₂-cyclopropyl;

R² is -CH₃ or -CH₂CH₃; and

X is N or CH,

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein X is N, or a pharmaceutically acceptable salt thereof.
3. The method of claim 1, wherein X is N, R¹ is -CH₂-cyclopropyl, and R² is -CH₂CH₃, or a pharmaceutically acceptable salt thereof.
4. The method of claim 1, wherein the compound is:

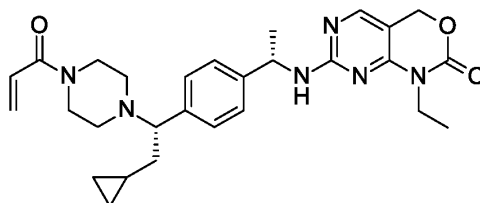
7-[[[(1S)-1-[4-[(1R)-2-Cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

7-[[[(1S)-1-[4-[(1S)-2-cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one; or

1-Ethyl-7-[[[(1S)-1-[4-[1-(4-prop-2-enoylpiperazin-1-yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one; or a pharmaceutically acceptable salt thereof.

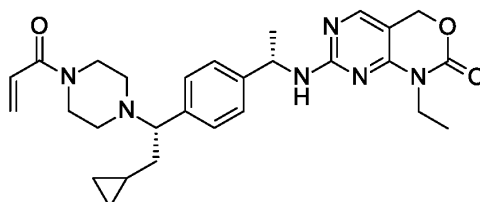
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5. The method of claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

6. The method of claim 5, wherein the compound is:



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7. The method of claim 1, wherein the cancer is a solid tumor cancer.
8. The method of claim 7, wherein the solid tumor cancer is
 cholangiocarcinoma, head and neck cancer, chondrosarcoma,
 hepatocellular carcinoma, melanoma, pancreatic cancer, astrocytoma,
 oligodendroglioma, glioma, glioblastoma, bladder carcinoma, colorectal
 cancer, lung cancer, or sinonasal undifferentiated carcinoma.
9. The method of claim 8, wherein the solid tumor cancer is
 cholangiocarcinoma.
10. The method of claim 1, wherein the cancer is a hematologic malignancy.
11. The method of claim 10, wherein the hematologic malignancy is acute
 myeloid leukemia, myelodysplastic syndrome myeloproliferative
 neoplasm, angioimmunoblastic T-cell lymphoma, T-cell acute
 lymphoblastic leukemia, polycythemia vera, essential thrombocythemia,
 primary myelofibrosis, or chronic myelogenous leukemia.
12. The method of claim 11, wherein the hematologic malignancy is acute
 myeloid leukemia.

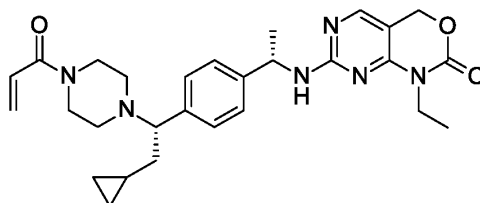
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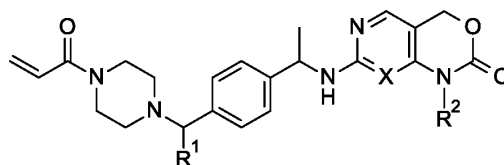
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13. The method of claim 1, wherein the compound is



and the cancer is acute myeloid leukemia.

14. The method of claim 1, wherein the one or more secondary IDH1 mutations is one or more of R119P, G131A, D279N, S280F, G289D or H315D.
15. The method of claim 13, wherein the one or more secondary IDH1 mutations is one or more of R119P, G131A, D279N, S280F, G289D or H315D.
16. The method of claim 1, wherein the human subject had been treated with an IDH1 inhibitor other than a compound of the formula:

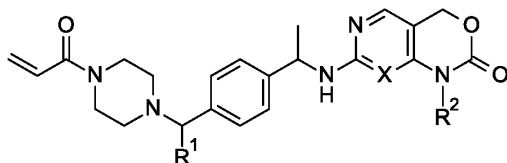


wherein:

- R¹ is -CH₂CH(CH₃)₂, -CH₂CH₃, -CH₂CH₂OCH₃, or -CH₂-cyclopropyl;
- R² is -CH₃ or -CH₂CH₃; and
- X is N or CH,
- or a pharmaceutically acceptable salt thereof.
17. The method of claim 16, wherein the human subject had been treated with ivosidenib.

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18. A compound of the Formula:



wherein:

R¹ is -CH₂CH(CH₃)₂, -CH₂CH₃, -CH₂CH₂OCH₃, or
-CH₂-cyclopropyl;

R² is -CH₃ or -CH₂CH₃; and

X is N or CH,

or a pharmaceutically acceptable salt thereof;

for use in treating cancer in a human subject having an IDH1 R132
mutation and one or more secondary IDH1 mutations.

19. The compound for use according to claim 18, wherein X is N, or a
pharmaceutically acceptable salt thereof.

20. The compound for use according to claim 18 or 19, wherein R¹ is -CH₂-
cyclopropyl, or a pharmaceutically acceptable salt thereof.

21. The compound for use according to any one of claim 18-20, wherein R² is
-CH₂CH₃, or a pharmaceutically acceptable salt thereof.

22. The compound for use according to claim 18, wherein the compound is:

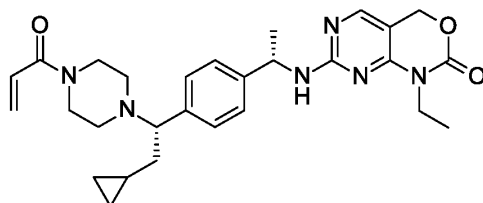
7-[[[(1S)-1-[4-[(1R)-2-Cyclopropyl-1-(4-prop-2-enoylpiperazin-1-
yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-
one;

7-[[[(1S)-1-[4-[(1S)-2-cyclopropyl-1-(4-prop-2-enoylpiperazin-1-
yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-
one; or

1-Ethyl-7-[[[(1S)-1-[4-[1-(4-prop-2-enoylpiperazin-1-
yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one;
or a pharmaceutically acceptable salt thereof.

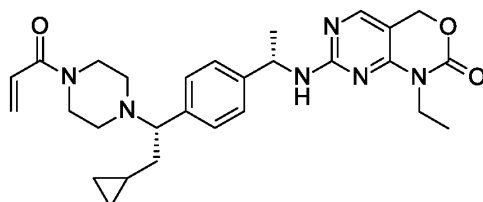
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23. The compound for use according to claim 18, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

24. The compound for use according to claim 23, wherein the compound is:



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25. The compound for use according to any one of claim 18-24, wherein the one or more secondary IDH1 mutations is one or more of R119P, G131A, D279N, S280F, G289D and H315D.

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26. The compound for use according to any one of claims 18-25, wherein the cancer is a solid tumor cancer.

27. The compound for use according to claim 26, wherein the solid tumor cancer is cholangiocarcinoma, head and neck cancer, chondrosarcoma, hepatocellular carcinoma, melanoma, pancreatic cancer, astrocytoma, oligodendroglioma, glioma, glioblastoma, bladder carcinoma, colorectal cancer, lung cancer, or sinonasal undifferentiated carcinoma.

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28. The compound for use according to claim 27, wherein the solid tumor cancer is cholangiocarcinoma.

29. The compound for use according to any one of claims 18-25, wherein the cancer is a hematologic malignancy.

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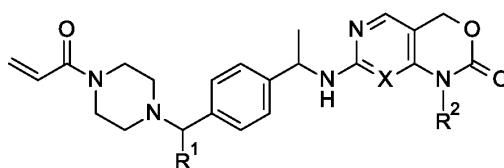
30. The compound for use according to claim 29, wherein the hematologic malignancy is acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative neoplasm, angioimmunoblastic T-cell lymphoma, T-cell acute lymphoblastic leukemia, polycythemia vera, essential

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thrombocythemia, primary myelofibrosis, or chronic myelogenous leukemia.

31. The compound for use according to claim 30, wherein the hematologic malignancy is acute myeloid leukemia.

5 32. The compound for use according to any one of claims 18-31, wherein the subject had been treated with a mutant IDH1 inhibitor other than a compound of the formula:



wherein:

10 R¹ is -CH₂CH(CH₃)₂, -CH₂CH₃, -CH₂CH₂OCH₃, or -CH₂-cyclopropyl;

R² is -CH₃ or -CH₂CH₃; and

X is N or CH, or a pharmaceutically acceptable salt thereof.

15 33. The compound for use according to claim 32, wherein the subject had been treated with ivosidenib.