

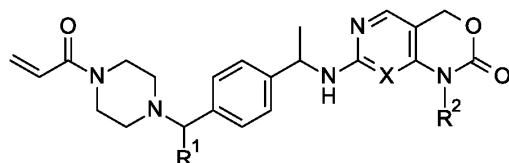
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WE CLAIM:

1. A method of treating cancer, comprising administering to a human cancer subject having an IDH mutation a therapeutically effective amount of

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(a) a first compound of the Formula:



wherein:

R^1 is $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, or $-\text{CH}_2$ -cyclopropyl;

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R^2 is $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$; and

X is N or CH,

or a pharmaceutically acceptable salt thereof; and

(b) a second compound that is a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof.

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2. The method of claim 1, wherein the IDH mutation is an IDH1 mutation.

3. The method of claim 2, wherein the IDH1 mutation is an IDH1 R132 mutation.

4. The method of claim 1, wherein the IDH mutation is an IDH2 mutation.

5. The method of claim 4, wherein the IDH2 mutation is an IDH2 R140 or IDH2 R172 mutation.

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6. The method of claim 1, wherein in the first compound, X is N, or a pharmaceutically acceptable salt thereof.

7. The method of claim 1, wherein in the first compound X is N, R^1 is $-\text{CH}_2$ -cyclopropyl, and R^2 is $-\text{CH}_2\text{CH}_3$, or a pharmaceutically acceptable salt thereof.

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

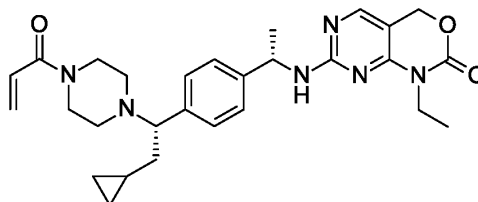
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7-[[[(1S)-1-[4-[(1R)-2-cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

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

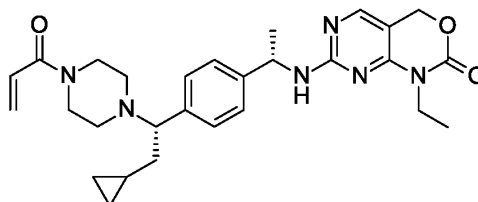
1-Ethyl-7-[[[(1S)-1-[4-[1-(4-prop-2-enoylpiperazin-1-yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one;
or a pharmaceutically acceptable salt thereof.

9. The method of claim 1, wherein the first compound is of the Formula:



or a pharmaceutically acceptable salt thereof.

10. The method of claim 9, wherein the first compound is:



11. The method of claim 1, wherein the cancer is a solid tumor cancer.

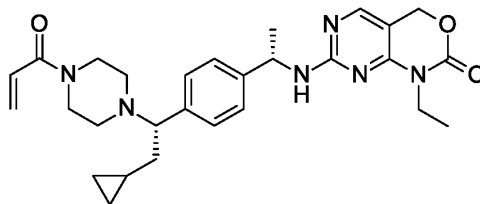
12. The method of claim 11, wherein the solid tumor cancer is cholangiocarcinoma, head and neck cancer, chondrosarcoma, hepatocellular carcinoma, melanoma, pancreatic cancer, astrocytoma, oligodendroglioma, glioma, glioblastoma, bladder carcinoma, colorectal cancer, sinonasal undifferentiated carcinoma, or lung cancer.

13. The method of claim 12, wherein the solid tumor cancer is cholangiocarcinoma.

14. The method of claim 1, wherein the cancer is a hematologic malignancy.

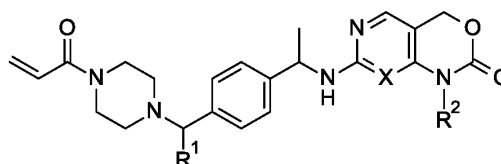
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15. The method of claim 14, wherein the hematologic malignancy is acute myeloid leukemia, myelodysplastic syndrome myeloproliferative neoplasm, angioimmunoblastic T-cell lymphoma, T-cell acute lymphoblastic leukemia, polycythemia vera, essential thrombocythemia, chronic myelogenous leukemia, or primary myelofibrosis.
16. The method of claim 15, wherein the hematologic malignancy is acute myeloid leukemia.
17. The method of claim 1, wherein the second compound is venetoclax, obatoclax, or navitoclax, or a pharmaceutically acceptable salt of any one of them.
18. The method of claim 1, wherein the first compound is



the second compound is venetoclax, and the cancer is acute myeloid leukemia.

19. 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,

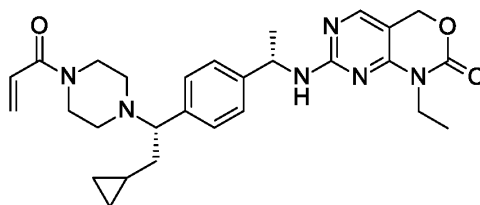
or a pharmaceutically acceptable salt thereof;

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for use in combination with a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof, in the treatment of cancer in a human subject having an IDH mutation.

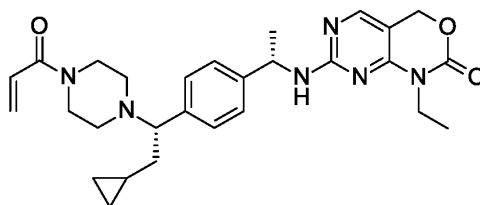
- 5 20. The compound for use of claim 20, wherein the IDH mutation is an IDH1 mutation.
21. The compound for use of claim 20, wherein the IDH1 mutation is an IDH1 R132 mutation.
22. The compound for use of claim 19, wherein the IDH mutation is an IDH2 mutation.
- 10 23. The compound for use of claim 22, wherein the IDH2 mutation is an IDH2 R140 or IDH2 R172 mutation.
24. The compound for use according to claim 19, wherein X is N, or a pharmaceutically acceptable salt thereof.
25. The compound for use according to claim 19 or 24, wherein R¹ is -CH₂-cyclopropyl, or a pharmaceutically acceptable salt thereof.
- 15 26. The compound for use according to any one of claims 19-25, wherein R² is -CH₂CH₃, or a pharmaceutically acceptable salt thereof.
27. The compound for use according to claim 19, wherein the compound is:
 7-[[[(1S)-1-[4-[(1R)-2-cyclopropyl-1-(4-prop-2-enoyl)piperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;
20 7-[[[(1S)-1-[4-[(1S)-2-cyclopropyl-1-(4-prop-2-enoyl)piperazin-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-enoyl)piperazin-1-yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one;
25 or a pharmaceutically acceptable salt thereof.
28. The compound for use according to claim 19, wherein the compound is:

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or a pharmaceutically acceptable salt thereof.

29. The compound for use according to claim 28, wherein the first compound is:



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30. The compound for use according to any one of claims 19-29, wherein the cancer is a solid tumor cancer.
31. The compound for use according to claim 30, 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, or lung cancer.
32. The compound for use according to claim 31, wherein the solid tumor cancer is cholangiocarcinoma.
33. The compound for use according to any one of claims 19-29, wherein the cancer is a hematologic malignancy.
34. The compound for use according to claim 33, 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, or primary myelofibrosis.
35. The compound for use according to claim 34, wherein the hematologic malignancy is acute myeloid leukemia.

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36. The compound for use according to any one of claims 19-35, wherein the Bcl-2 inhibitor is selected from the group consisting of venetoclax, obatoclax, navitoclax, or a pharmaceutically acceptable salt thereof.