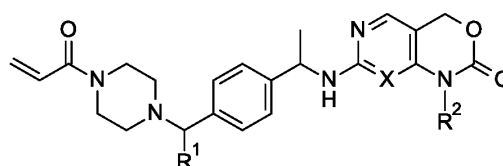


WE CLAIM:

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

5 (a) a first compound of the Formula:



wherein:

10 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;

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

15 (b) one or more of a second compound that is an antimetabolite agent, or a pharmaceutically acceptable salt thereof; a hypomethylating agent, or a pharmaceutically acceptable salt thereof; or a mutant Flt3 inhibitor, or a pharmaceutically acceptable salt thereof.

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

20 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.

25 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 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.

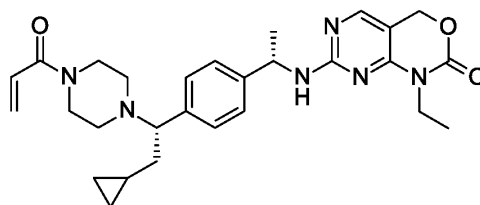
8. The method of claim 1, wherein the first compound is:

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

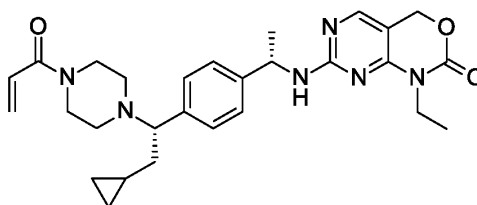
1-Ethyl-7-[[[(1S)-1-[4-[1-(4-prop-2-enoylpiperazin-1-yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one;
or a pharmaceutically acceptable salt thereof.

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:



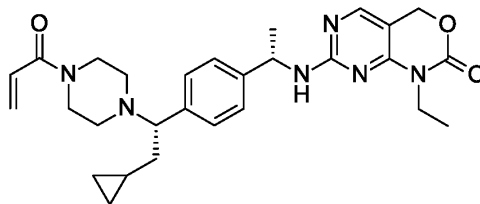
11. The method of claim 1, wherein the cancer is a solid tumor cancer.

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, lung cancer, or sinonasal undifferentiated carcinoma.

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

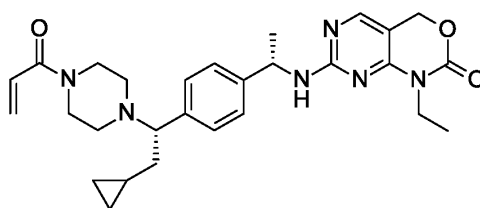
14. The method of claim 1, wherein the cancer is a hematologic malignancy.

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, chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis, or chronic myelogenous leukemia.
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 an antimetabolite agent, or a pharmaceutically acceptable salt thereof.
18. The method of claim 17, wherein the antimetabolite agent is cytarabine, or a pharmaceutically acceptable salt thereof.
19. The method of claim 1, wherein the first compound is



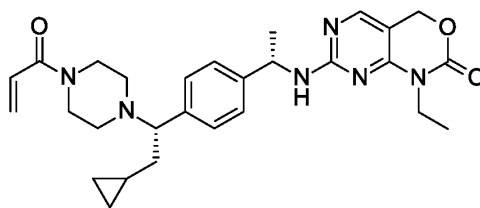
- the cancer is acute myeloid leukemia, and the second compound agent is cytarabine.
20. The method of claim 1, wherein the second compound is a hypomethylating agent, or a pharmaceutically acceptable salt thereof.
21. The method of claim 20, further comprising administering to the human cancer subject a therapeutically effective amount of a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof.
22. The method of claim 20, wherein the hypomethylating agent is azacitidine, or a pharmaceutically acceptable salt thereof.
23. The method of claim 22, further comprising administering to the human cancer subject a therapeutically effective amount of venetoclax, or a pharmaceutically acceptable salt thereof.
24. The method of claim 1, wherein the first compound is

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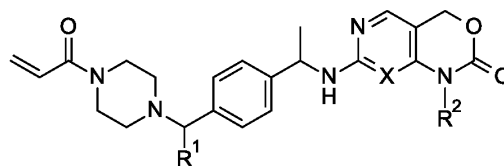
the cancer is acute myeloid leukemia, and the second compound is azacitidine.

25. The method of claim 24, further comprising administering to the human cancer subject a therapeutically effective amount of venetoclax.
26. The method of claim 24, wherein the mutant Flt3 inhibitor is midostaurin, or a pharmaceutically acceptable salt thereof.
27. The method of claim 1, wherein the first compound is



the cancer is acute myeloid leukemia, and the mutant Flt3 inhibitor is midostaurin.

28. 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 combination with one or more of an antimetabolite agent, or a pharmaceutically acceptable salt thereof; a hypomethylating agent, or a pharmaceutically acceptable salt thereof; or a mutant Flt3 inhibitor, or a pharmaceutically acceptable salt thereof,

5 in the treatment of cancer in a human subject having an IDH mutation.

29. The compound for use of claim 28, wherein the IDH mutation is an IDH1 mutation.

10 30. The compound for use of claim 29, wherein the IDH1 mutation is an IDH1 R132 mutation.

31. The compound for use of claim 28, wherein the IDH mutation is an IDH2 mutation.

32. The compound for use of claim 31, wherein the IDH2 mutation is an IDH2 R140 or IDH2 R172 mutation.

15 33. The compound for use according to claim 28, wherein X is N, or a pharmaceutically acceptable salt thereof.

34. The compound for use according to claim 28 or 33, wherein R¹ is -CH₂-cyclopropyl, or a pharmaceutically acceptable salt thereof.

20 35. The compound for use according to any one of claims 28, 33 or 34, wherein R² is -CH₂CH₃, or a pharmaceutically acceptable salt thereof.

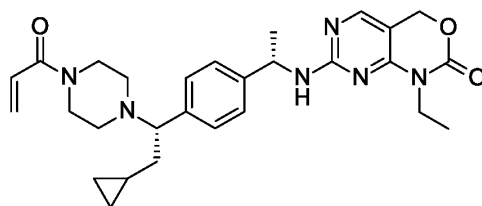
36. The compound for use according to claim 28, wherein the compound is:
7-[[[(1S)-1-[4-[(1R)-2-Cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

25 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 (Compound A); or

30 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.

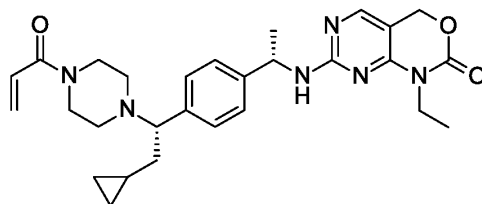
37. The compound for use according to claim 28, wherein the compound is:

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or a pharmaceutically acceptable salt thereof.

38. The compound for use according to claim 37, wherein the compound is:



- 5 39. The compound for use according to any one of claims 28-38, wherein the cancer is a solid tumor cancer.
40. The compound for use according to claim 39, 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.
- 10 41. The compound for use according to claim 40, wherein the solid tumor cancer is cholangiocarcinoma.
42. The compound for use according to any one of claims 28-38, wherein the cancer is a hematologic malignancy.
- 15 43. The compound for use according to claim 42, 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.
- 20 44. The compound for use according to claim 43, wherein the hematologic malignancy is acute myeloid leukemia.

45. The compound for use according to any one of claims 28-44, for use in combination with an antimetabolite agent.
46. The compound for use according to claim 45, wherein the antimetabolite agent is cytarabine, or a pharmaceutically acceptable salt thereof.
- 5 47. The compound for use according to any one of claims 28-44, for use in combination with a hypomethylating agent.
48. The compound for use according to claim 47, in further combination with a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof.
49. The compound for use according to claim 47, wherein the
10 hypomethylating agent is azacitidine, or a pharmaceutically acceptable salt thereof.
50. The compound of use of claim 48, in combination with venetoclax, or a pharmaceutically acceptable salt thereof.
51. The compound for use according to claim 49, in combination with
15 venetoclax.
52. The compound for use according to claim 28, wherein the mutant Flt3 inhibitor is midostaurin, or a pharmaceutically acceptable salt thereof.