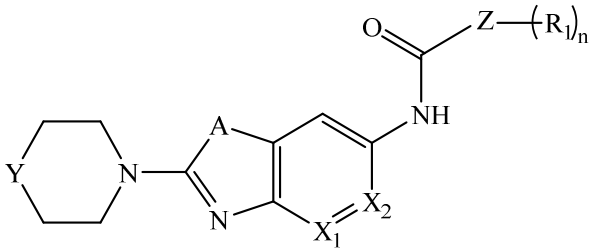
CLAIMS:

1. Use of a compound in the manufacture of a medicament for the treatment of acute myeloid leukemia (AML) associated with a mutation in FLT-3 kinase, wherein the compound is represented by formula II:



(II)

or a pharmaceutically acceptable salt thereof;

wherein

X_1 is CH and X_2 is N or X_1 is N and X_2 is CR_2;

A is O or S;

Y is $-CH_2-$ or O;

Z is a heterocyclyl comprising a nitrogen;

R_1 is an optionally substituted heterocyclyl comprising a nitrogen; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$;

R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or $-NR_aR_b$; wherein the substituent is alkyl, amino, halo or hydroxyl;

R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl; and

n is 1.

2. The use of claim 1, wherein

A is O or S;

Y is $-CH_2-$ or O;

Z is a heterocyclyl comprising a nitrogen;

R_1 is an optionally substituted heterocyclyl comprising a nitrogen, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; and

n is 1.

3. The use of claim 1, wherein

A is O or S;

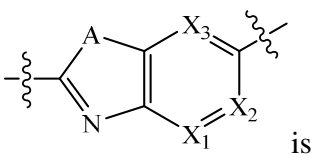
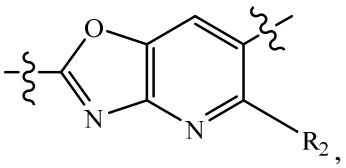
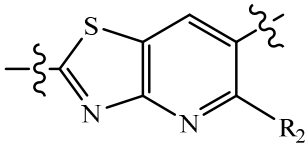
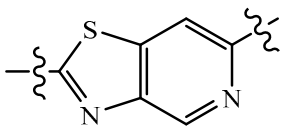
Y is -CH_2- or O;

Z is a heterocyclyl comprising a nitrogen;

R_1 is a optionally substituted heterocyclyl comprising a nitrogen; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

n is 1.

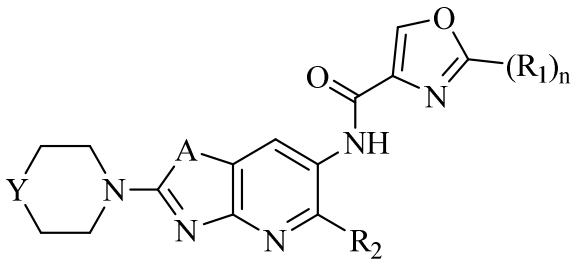
4. The use of claim 1, wherein  is , , or .

5. The use of any one of claims 1-4, wherein Z is a 5- or 6-membered heterocyclyl comprising a nitrogen.

6. The use of any one of claims 1-4, wherein Z is an optionally substituted heterocyclyl comprising a nitrogen selected from pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, azetidinyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl,

pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, and azabicyclo[3.2.1]octanyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; and R_a and R_b are independently hydrogen, alkyl or acyl.

7. The use of claim 1, wherein the compound represented by formula II is represented by formula (IIA):



(IIA)

or a pharmaceutically acceptable salt thereof.

8. The use of claim 7, wherein

A is O or S;

Y is $-CH_2-$ or O;

R_1 is an optionally substituted heterocyclyl comprising a nitrogen, wherein the substituent is alkyl, aminoalkyl, halo, or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, heterocyclyl or $-NR_aR_b$;

'm' is 0; and

'n' is 1.

9. The use of claim 7, wherein

A is O or S;

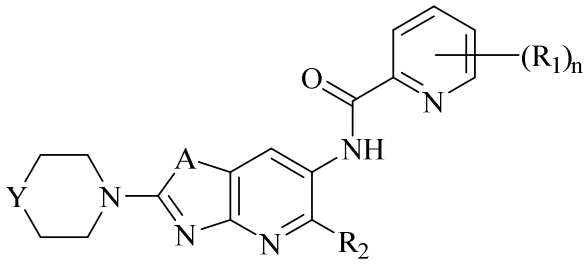
Y is $-CH_2-$ or O;

R_1 is an optionally substituted heterocyclyl comprising a nitrogen ; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $-NR_aR_b$, where the substituent is selected from amino, halo or hydroxyl; and

n is 1.

10. The use of claim 1, wherein the compound represented by formula II is represented by formula (IIB):



(IIB)

or a pharmaceutically acceptable salt thereof.

11. The use of claim 10, wherein

A is O or S;

Y is $-CH_2-$ or O;

R_1 is an optionally substituted heterocyclyl comprising a nitrogen, wherein the substituent is alkyl, aminoalkyl, halo, or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, heterocyclyl or $-NR_aR_b$; and

'n' is 1.

12. The use of claim 10, wherein

A is O or S;

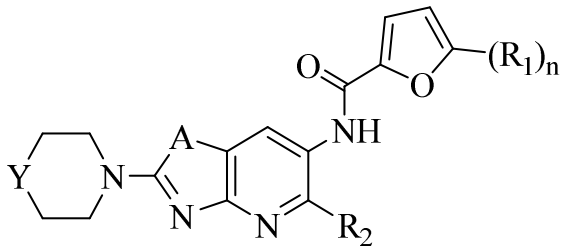
Y is $-CH_2-$ or O;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

'm' and 'n' are independently 0, 1 or 2.

13. The use of claim 1, wherein the compound represented by formula II is represented by formula (IIC)



(IIC)

or a pharmaceutically acceptable salt thereof.

14. The use of any one of claims 1-13, wherein R_1 is optionally substituted heterocyclyl comprising a nitrogen; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; and R_a and R_b are independently hydrogen or acyl.

15. The use of any one of claims 1-13, wherein R_1 is optionally substituted heterocyclyl comprising a nitrogen; wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; and R_a and R_b are independently hydrogen or acyl.

16. The use of any one of claims 1-13, wherein R_1 is optionally substituted heterocyclyl comprising a nitrogen; and the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.

17. The use of any one of claims 1-13, wherein R_1 is optionally substituted heterocyclyl comprising a nitrogen; and the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.

18. The use of any one of claims 14-17, wherein R_1 is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl.

19. The use of any one of claims 14-17, wherein R_1 is optionally substituted pyrazolyl, wherein the substituent is alkyl, hydroxyl or -NR_aR_b.

20. The use of claim 13, wherein R_2 is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b.

21. The use of any one of claims 1-20, wherein R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl.

22. The use of any one of claims 1-20, wherein R_2 is optionally substituted heterocyclyl selected from piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidinyl, pyrazolyl, furanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is hydroxyl, halo, alkyl or amino.

23. The use of any one of claims 1-20, wherein R_2 is piperidinyl, pyrrolidinyl, morpholinyl, or piperazinyl.

24. The use of any one of claims 1-20, wherein R_2 is hydrogen.

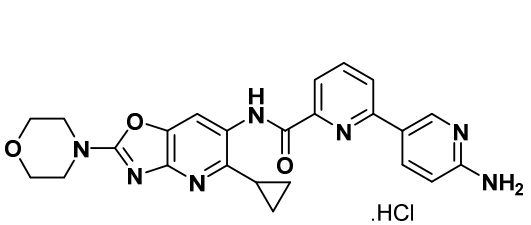
25. The use of any one of claims 1-20, wherein R_2 is cycloalkyl.

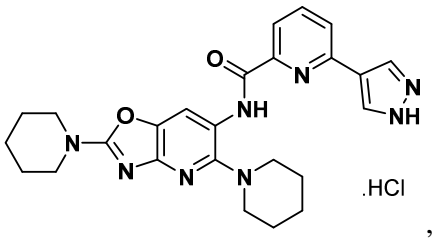
26. The use of claim 25, wherein R_2 is cyclopropyl.

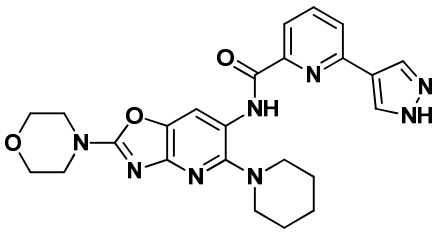
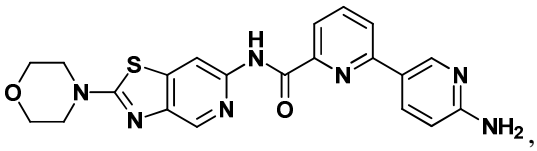
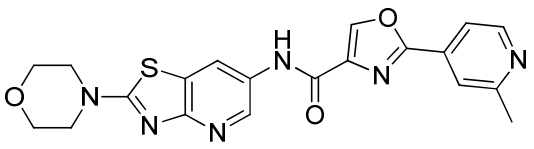
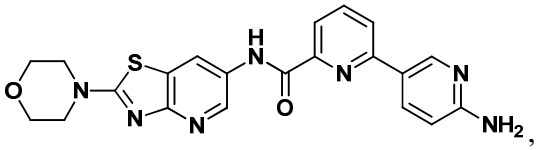
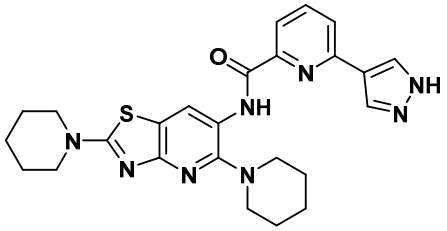
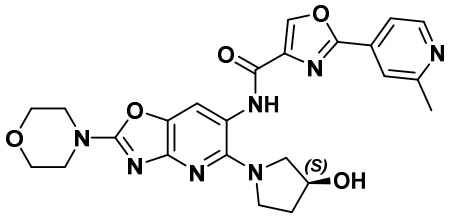
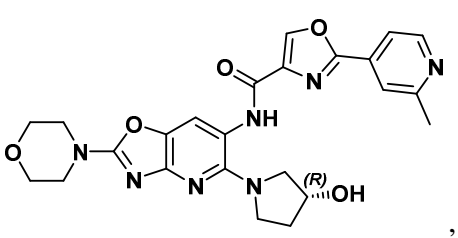
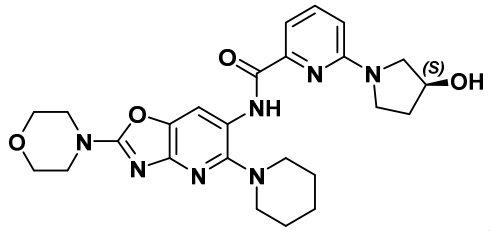
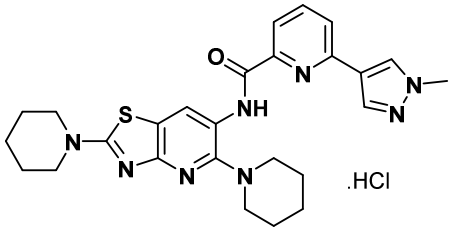
27. The use of any one of claims 1-26, wherein R_3 is alkyl.

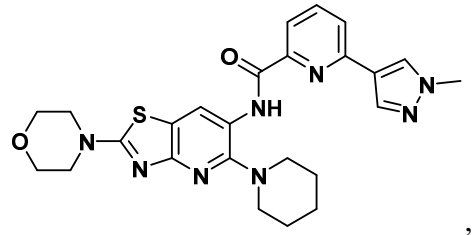
28. The use of any one of claims 1-27, wherein m is 0 and p is 1.

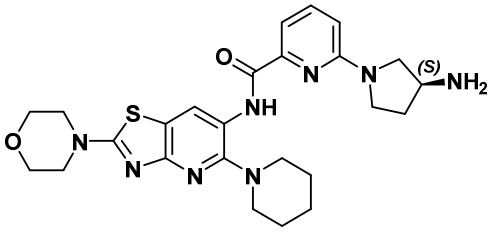
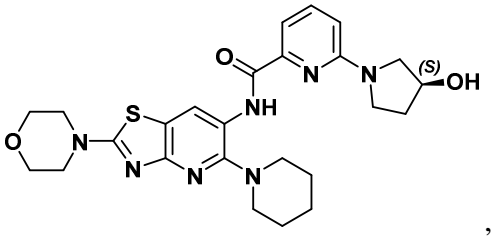
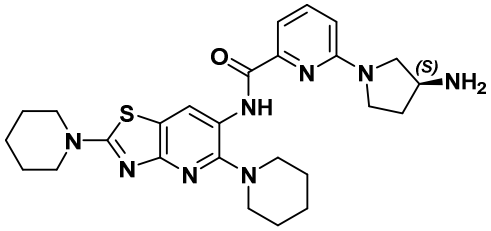
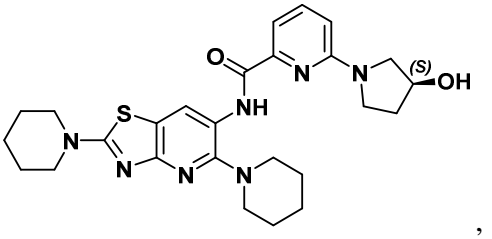
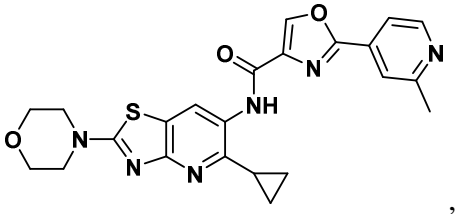
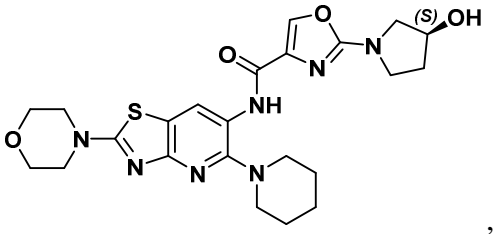
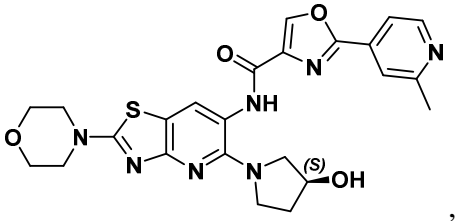
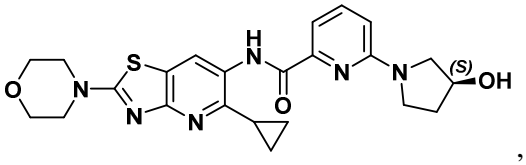
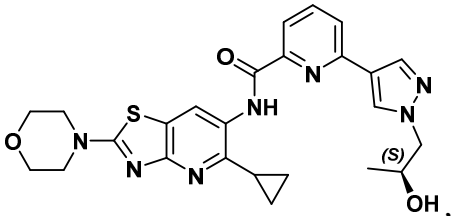
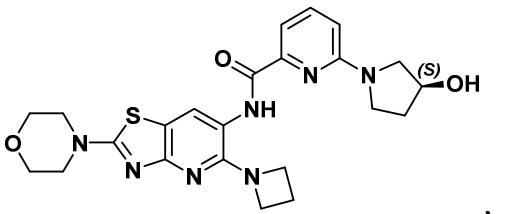
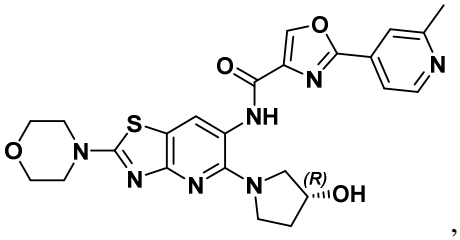
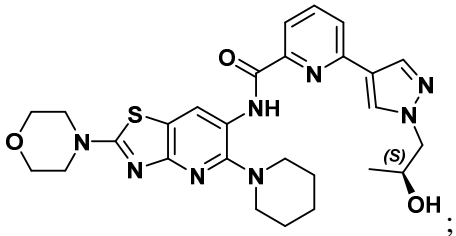
29. The use of claim 1, wherein the compound represented by formula (II) is selected from:



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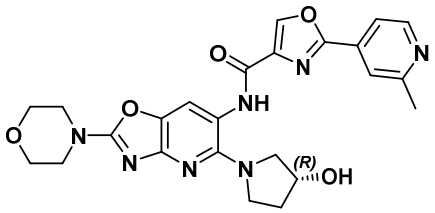
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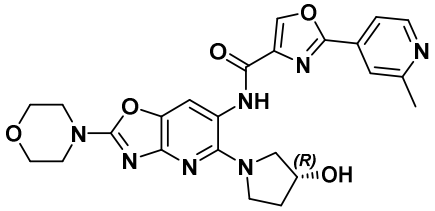
or a pharmaceutically acceptable salt thereof.

30. The use of claim 1, wherein the compound represented by formula (II) is



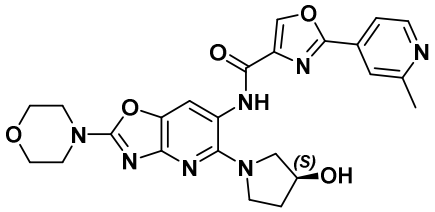
or a pharmaceutically acceptable salt thereof.

31. The use of claim 1, wherein the compound represented by formula (II) is



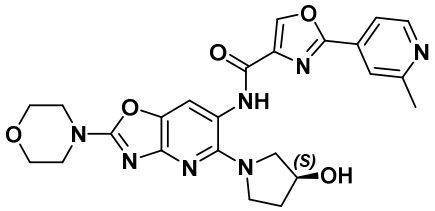
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32. The use of claim 1, wherein the compound represented by formula (II) is



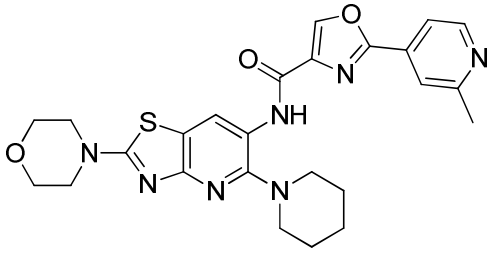
or a pharmaceutically acceptable salt thereof.

33. The use of claim 1, wherein the compound represented by formula (II) is



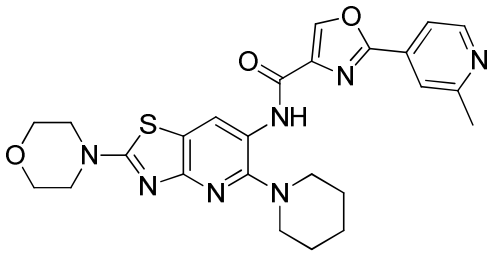
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34. The use of claim 1, wherein the compound represented by formula (II) is



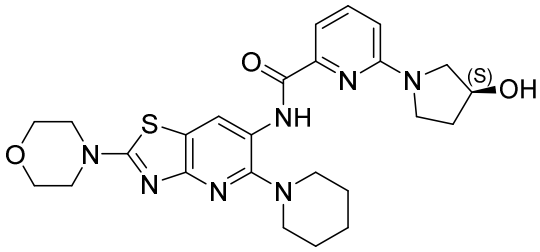
or a pharmaceutically acceptable salt thereof.

35. The use of claim 1, wherein the compound represented by formula (II) is



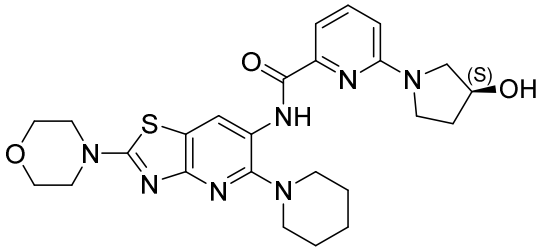
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36. The use of claim 1, wherein the compound represented by formula (II) is



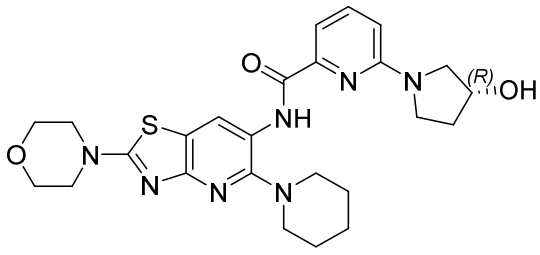
or a pharmaceutically acceptable salt thereof.

37. The use of claim 1, wherein the compound represented by formula (II) is



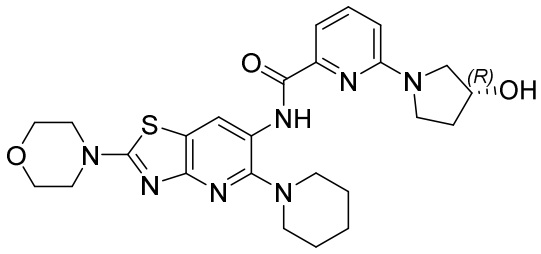
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38. The use of claim 1, wherein the compound represented by formula (II) is



or a pharmaceutically acceptable salt thereof.

39. The use of claim 1, wherein the compound represented by formula (II) is



.

40. The use of any one of claims 1-39, wherein the mutation is an internal tandem duplication (ITD).

41. The use of any one of claims 1-39, wherein the mutation is selected from D835H, D835V, D835Y, K663Q, N841I, ITD and D835V, and ITD and F691L.

42. The use of any one of claims 1-41, wherein the AML is resistant to an FLT-3 inhibitor.