R^2 represents hydrogen or halo;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;
or a pharmaceutically acceptable salt or a solvate thereof.

The present disclosure also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, and a pharmaceutically acceptable carrier or excipient. The present disclosure, in another aspect, relates to a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier or diluent.

Additionally, the disclosure relates to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use as a medicament, and to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or in the prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

The present disclosure, in another aspect, relates to a compound as defined herein or a pharmaceutical composition as defined herein for use as a medicament.

In a particular example, the disclosure relates to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or in the prevention of cancer. The present disclosure, in another aspect, relates to a compound as defined herein or a pharmaceutical composition as defined herein for use in the prevention or treatment of cancer.

In a specific examplesaid cancer is selected from leukemias, lymphomas, myelomas or solid tumor cancers (e.g. prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma, etc.). In some examples, the leukemias include acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, leukemias exhibiting *HOX*/*MEIS1* gene expression signatures etc.

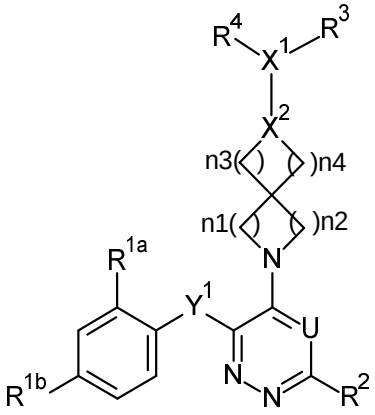
In particular, compounds according to the present disclosure and the pharmaceutical compositions thereof may be useful in the treatment or prevention of leukemias, in particular nucleophosmin (NPM1)-mutated leukemias, e.g. NPM1c. The present disclosure, in another aspect, relates to a compound as defined herein or a pharmaceutical composition as defined herein for use in the prevention or treatment of leukemia, myelodysplastic syndrome (MDS), or myeloproliferative neoplasms (MPN).

The present disclosure, in another aspect, relates to use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating or preventing a discorder selected from cancer.

The present disclosure, in another aspect, relates to use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating or preventing leukemia, myelodysplastic syndrome (MDS), or myeloproliferative neoplasms (MPN).

CLAIMS

1. A compound of Formula (I)



(I)

,

or a tautomer or a stereoisomeric form thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$ or Het;

Het represents a 6-membered monocyclic aromatic ring containing two nitrogen atoms; wherein said 6-membered monocyclic aromatic ring is substituted with one C_{3-6}cycloalkyl;
R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen or halo;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, wherein R^2 represents hydrogen.

3. The compound according to claim 1 or 2, wherein

U represents N;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl.

4. The compound according to claim 3, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

U represents N;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, or -C_{1-6}alkyl-OH;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl.

5. The compound according to claim 1 or 2, wherein

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

6. The compound according to claim 1 or 2, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

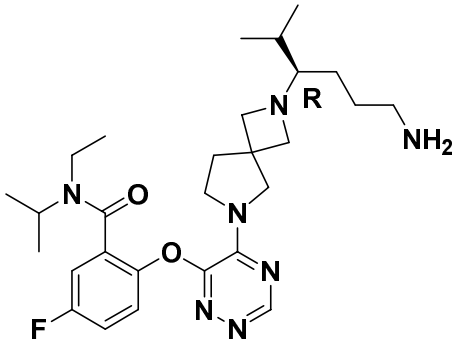
U represents N;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$;

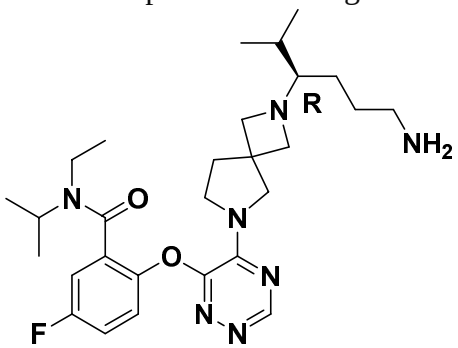
R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

7. The compound according to claim 1 or 2, wherein the compound is



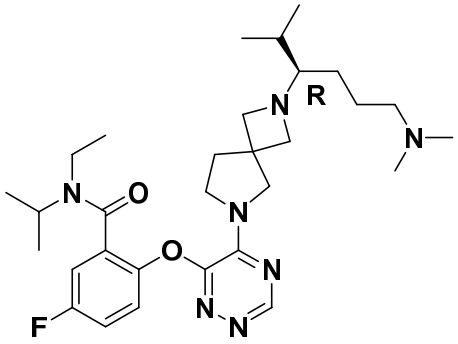
or a pharmaceutically acceptable salt or a solvate thereof.

8. The compound according to claim 7, wherein the compound is



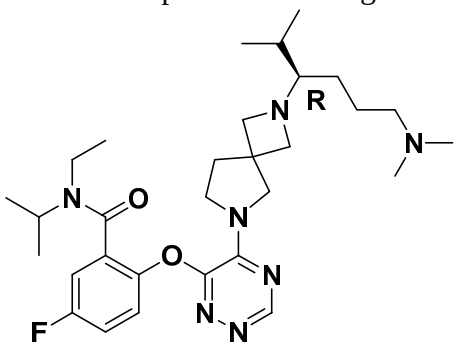
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9. The compound according to claim 1 or 2, wherein the compound is



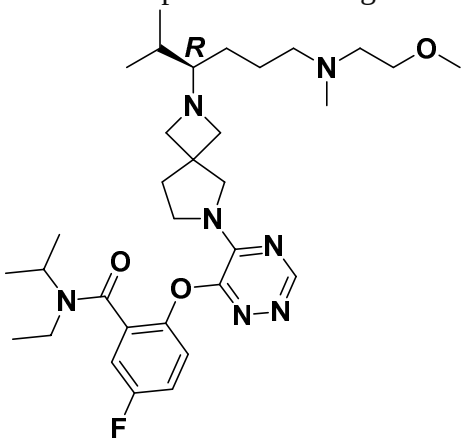
or a pharmaceutically acceptable salt or a solvate thereof.

10. The compound according to claim 9, wherein the compound is



.

11. The compound according to claim 1 or 2, wherein the compound is



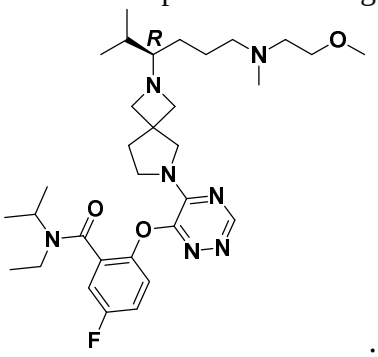
or a pharmaceutically acceptable salt or a solvate thereof.

12. The compound according to claim 11, wherein the compound is a pharmaceutically acceptable salt.

13. The compound according to claim 11, wherein the compound is a solvate.

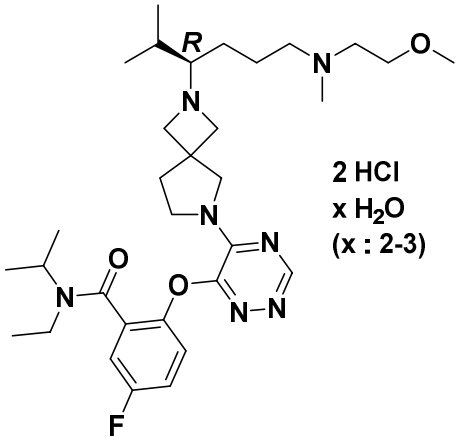
14. The compound according to claim 11, wherein the compound is a solvate of a pharmaceutically acceptable salt.

15. The compound according to claim 11, wherein the compound is

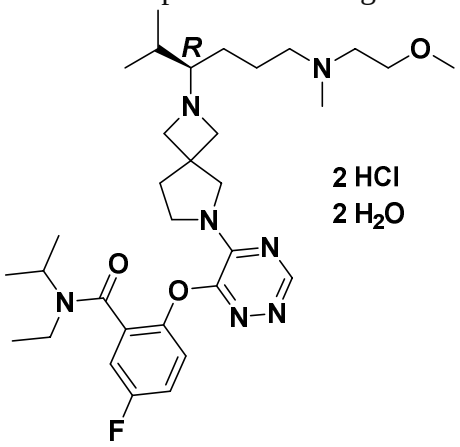


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16. The compound according to claim 11, wherein the compound is

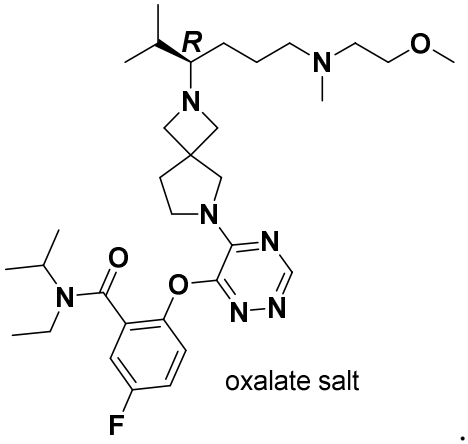


17. The compound according to claim 16, wherein the compound is



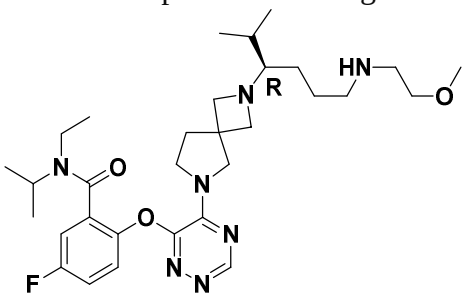
.

18. The compound according to claim 14, wherein the compound is



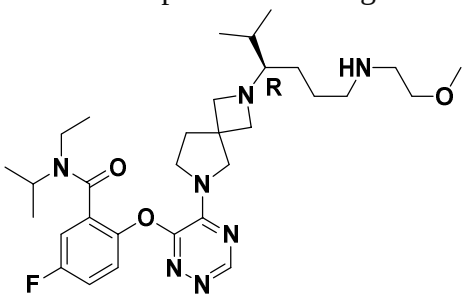
.

19. The compound according to claim 1 or 2, wherein the compound is



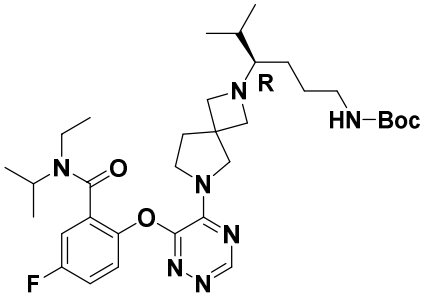
or a pharmaceutically acceptable salt or a solvate thereof.

20. The compound according to claim 19, wherein the compound is



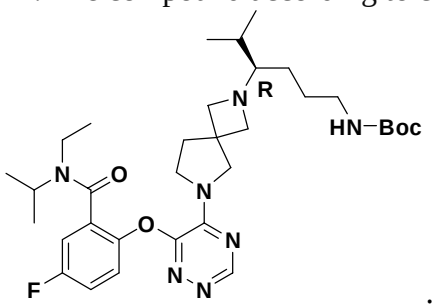
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21. The compound according to claim 1 or 2, wherein the compound is



or a pharmaceutically acceptable salt or a solvate thereof.

22. The compound according to claim 21, wherein the compound is

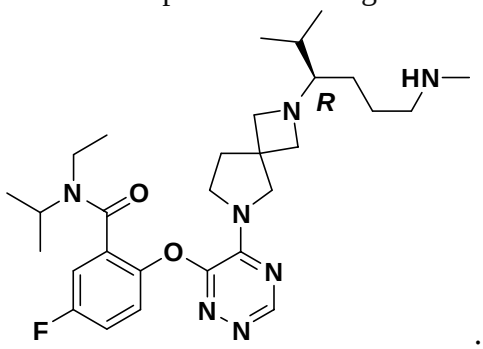


.

23. The compound according to claim 1 or 2, wherein the compound is

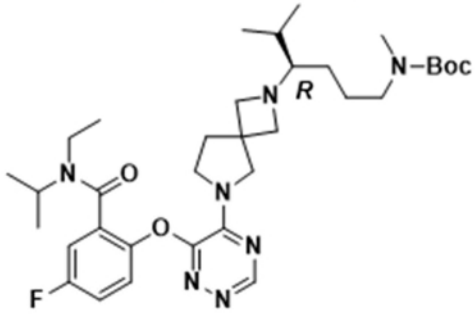
or a pharmaceutically acceptable salt or a solvate thereof.

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



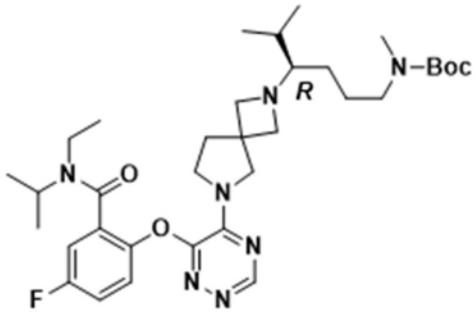
.

25. The compound according to claim 1 or 2, wherein the compound is



or a pharmaceutically acceptable salt or a solvate thereof.

26. The compound according to claim 25, wherein the compound is

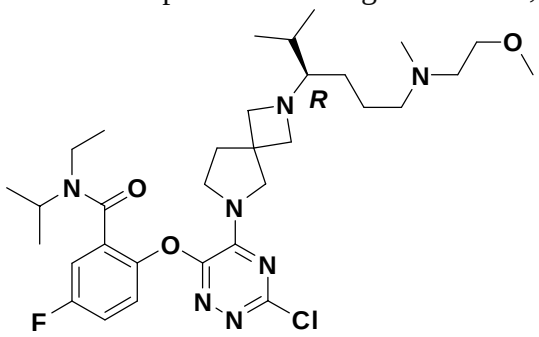


.

27. The compound according to claim 1, wherein the compound is

or a pharmaceutically acceptable salt or a solvate thereof.

28. The compound according to claim 27, wherein the compound is

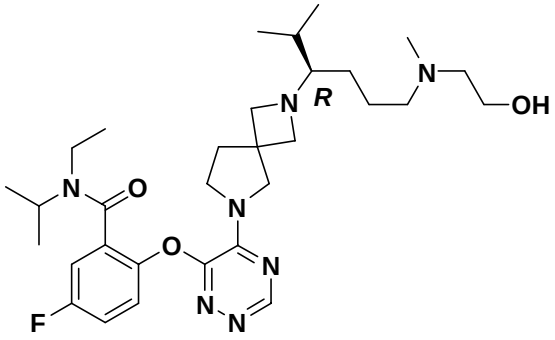


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29. The compound according to claim 1 or 2, wherein the compound is

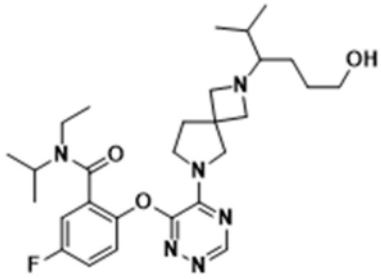
or a pharmaceutically acceptable salt or a solvate thereof.

30. The compound according to claim 29, wherein the compound is



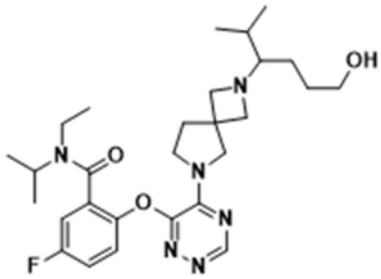
.

31. The compound according to claim 1 or 2, wherein the compound is



or a pharmaceutically acceptable salt or a solvate thereof.

32. The compound according to claim 31, wherein the compound is



.

33. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 32 and a pharmaceutically acceptable carrier or diluent.

34. A process for preparing a pharmaceutical composition according to claim 33 comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound according to any one of claims 1 to 32.

35. A compound as claimed in any one of claims 1 to 32 or a pharmaceutical composition as claimed in claim 33 for use as a medicament.

36. A compound as claimed in any one of claims 1 to 32 or a pharmaceutical composition as claimed in claim 33 for use in the prevention or treatment of cancer.

37. A compound as claimed in any one of claims 1 to 32 or a pharmaceutical composition as claimed in claim 33 for use in the prevention or treatment of leukemia, myelodysplastic syndrome (MDS), or myeloproliferative neoplasms (MPN).

38. The compound or the pharmaceutical composition for use according to claim 37 in the prevention or treatment of leukemia wherein the leukemia is (*NPM1*)-mutated leukemia.

39. The compound or the pharmaceutical composition for use according to claim 36, wherein cancer is selected from leukemias, lymphomas, myelomas or solid tumor cancers such as prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma.

40. The compound or the pharmaceutical composition for use according to claim 37, in the prevention or treatment of leukemia wherein the leukemia is selected from acute leukemias, chronic leukemias, myeloid leukemias, myelogenous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), *KMT2A*-rearranged leukemias, *KMT2A*-PTD leukemias, *KMT2A* amplified leukemias, *KMT2A*-positive leukemias, and leukemias exhibiting *HOX*/*MEIS1* gene expression signatures.

41. Use of a compound as claimed in any one of claims 1 to 32 or a pharmaceutical composition as claimed in claim 33 in the manufacture of a medicament for treating or preventing a disorder selected from cancer.

42. Use of a compound as claimed in any one of claims 1 to 32 or a pharmaceutical composition as claimed in claim 33 in the manufacture of a medicament for treating or preventing leukemia, myelodysplastic syndrome (MDS), or myeloproliferative neoplasms (MPN).

43. The use according to claim 42 wherein the leukemia is (NPM1)-mutated leukemia.

44. The use according to claim 41 wherein cancer is selected from leukemias, lymphomas, myelomas or solid tumor cancers such as prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma.

45. The use according to claim 42 wherein the leukemia is selected from acute leukemias, chronic leukemias, myeloid leukemias, myelogenous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogenous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), *KMT2A*-rearranged leukemias, *KMT2A*-PTD leukemias, *KMT2A* amplified leukemias, *KMT2A*-positive leukemias, and leukemias exhibiting *HOX/MEIS1* gene expression signatures.

46. The compound or the pharmaceutical composition for use according to claim 37 or the use of claim 42, in the prevention or treatment of leukemia wherein the leukemia is an acute leukemia.

47. The compound or the pharmaceutical composition for use or the use according to claim 45, in the treatment of an acute leukemia wherein the acute leukemia is AML or ALL.

48. The compound or the pharmaceutical composition for use or the use according to claim 47, in the treatment of an acute leukemia wherein the acute leukemia is AML.

49. The compound or the pharmaceutical composition for use or the use according to claim 47, in the treatment of an acute leukemia wherein the acute leukemia is ALL.

50. The compound or the pharmaceutical composition for use or the use according to any one of claims 46 to 49, wherein the acute leukemia has KMT2A gene alterations or *NPM1* mutations.

51. The compound or the pharmaceutical composition for use or the use according to any one of claims 46 to 49, wherein the acute leukemia has *KMT2A* rearrangements.

52. The compound or the pharmaceutical composition for use or the use according to any one of claims 46 to 49, wherein the acute leukemia has *NPM1* mutations.

53. The compound or the pharmaceutical composition for use according to claim 38, or the use according to claim 43, wherein the (*NPM1*)-mutated leukemia is (*NPM1c*)-mutated leukemia.

54. The compound or the pharmaceutical composition for use or the use according to claim 52, wherein the *NPM1* mutation is *NPM1*c.