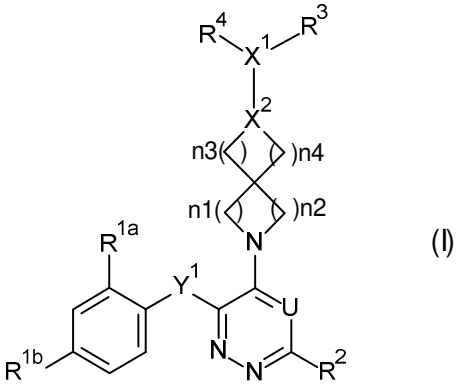
CLAIMS

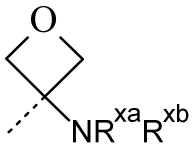
1. A compound of Formula (I)



(I)

,

or a tautomer or a stereoisomeric form thereof, wherein

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

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;
wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;
R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and -$NR^{7a}R^{7b}$;

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^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

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 substituents each independently selected from the group consisting of cyano, halo, -OH, and -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, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, 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^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 substituents each independently selected from the group consisting of cyano, halo or -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, -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.

3. The compound according to claim 2, 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 optionally 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 is hydrogen;

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 2, wherein

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

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 is hydrogen;

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, 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;

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 substituents each independently selected from the group consisting of -OH and -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, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

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

6. The compound according to claim 1, 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;

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-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of -OH and -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 -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -$C(=O)$-$NR^{10a}R^{10b}$, and -NR^{10c}-$C(=O)$-C_{1-4}alkyl;

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

7. The compound according to claim 1, wherein

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

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

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-$NR^{8a}R^{8b}$;

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 -OH, 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.

8. The compound according to claim 1, wherein
Y^1 represents -O-.

9. The compound according to claim 1, wherein
R^{1b} represents F.

10. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9 and a pharmaceutically acceptable carrier or diluent.

11. A process for preparing a pharmaceutical composition as defined in claim 10 comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound according to any one of claims 1 to 9.

12. A compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 for use as a medicament.

13. A compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 for use in the prevention or treatment of cancer.

14. A compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 for use in the prevention or treatment of leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN).

15. The compound or a pharmaceutical composition for use according to claim 14 in the prevention or treatment of leukemia wherein the leukemia is (NPM1)-mutated leukemia.

16. The compound or a pharmaceutical composition for use according to claim 13, 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.

17. The compound or a pharmaceutical composition for use according to claim 14, in the prevention or treatment of leukemia wherein the leukemia is selected from 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, and leukemias exhibiting *HOX*/*MEIS1* gene expression signatures.

18. Use of a compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 in the manufacture of a medicament for treating or preventing a discorder selected from cancer.

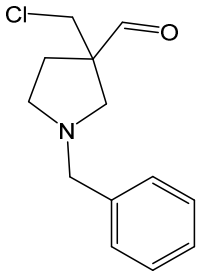
19. Use of a compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 in the manufacture of a medicament for treating or preventing leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN).

20. The use according to claim 19 wherein the leukemia is (NPM1)-mutated leukemia.

21. The use according to claim 18 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.

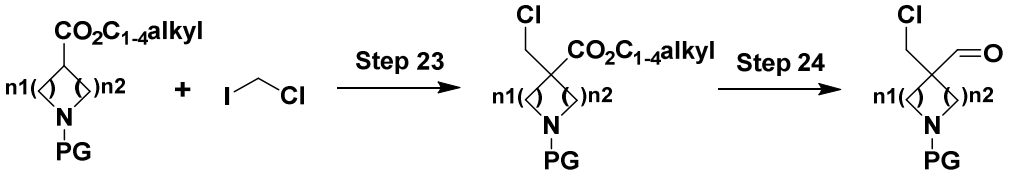
22. The use according to claim 19 wherein the leukemia is selected from acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (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, and leukemias exhibiting *HOX/MEIS1* gene expression signatures.

23. An intermediate with the structure



or a tautomer or a stereoisomeric form thereof ;
or a pharmaceutically acceptable addition salt or a solvate thereof.

24. A process for the preparation of an intermediate comprising the following steps:



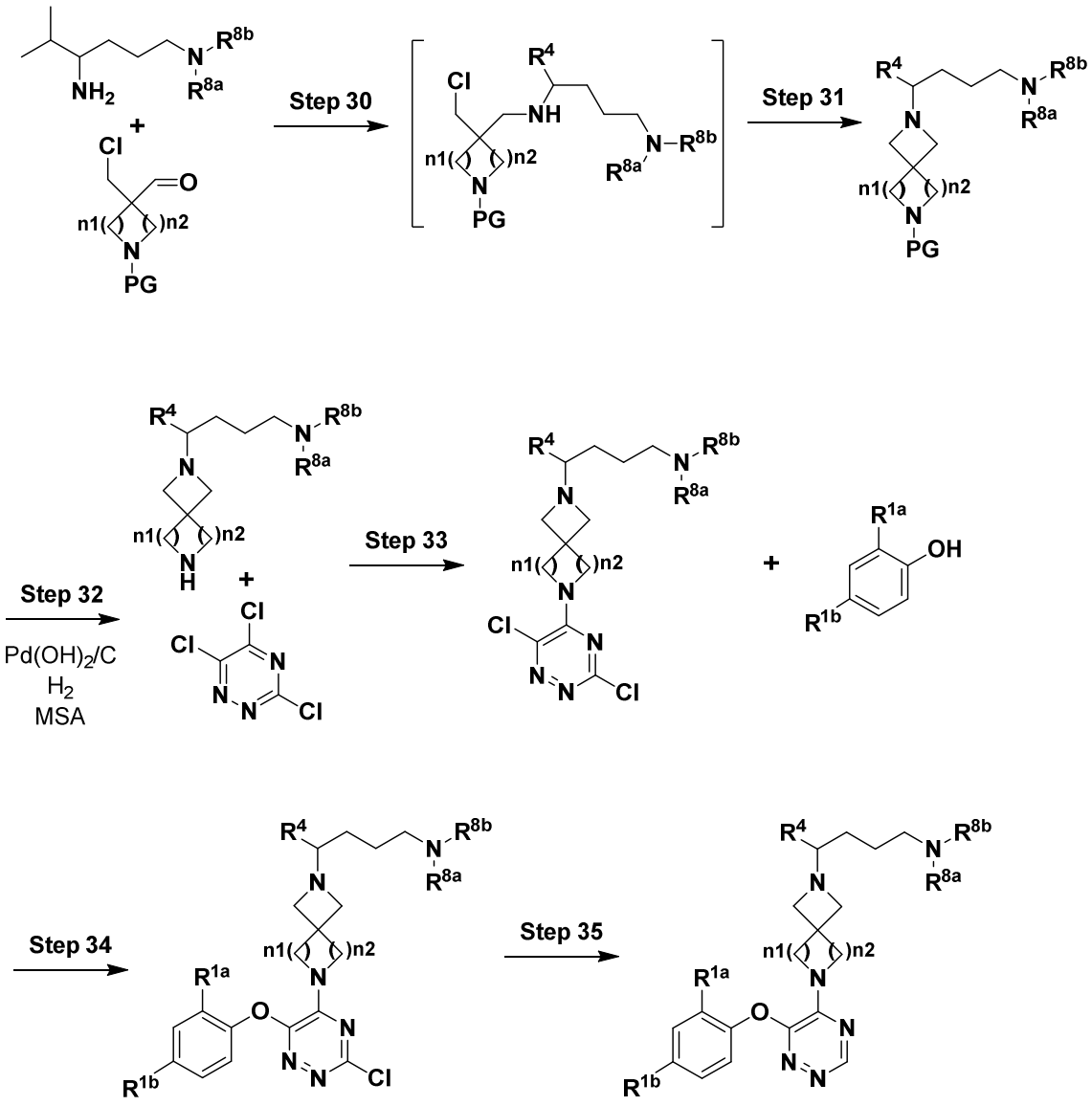
wherein PG is a suitable protecting group such as benzyl;

wherein n1 and n2 are as defined for formula (I);

Step 23: at a suitable temperature such as for example from -78 °C to -25 °C, in the presence of suitable bases such as for example DIEA and n-BuLi, in a suitable solvent such as for example THF;

Step 24: at a suitable temperature such as for example between -55°C and -65 °C, in the presence of suitable reducing agent such as for example DIBAL-H, in a suitable solvent such as for example toluene, conducted in a suitable flow chemistry system.

25. A process for the preparation of an intermediate comprising the following steps:



PG is a suitable protecting group such as benzyl;

other variables are as defined for formula (I);

Step 30: at a suitable temperature such as for example from 5 ºC to 30 ºC, in the presence of a suitable base such as for example TEA, in the presence of suitable reducing agent such as for example $NaBH(OAc)_3$, in a suitable solvent such as for example toluene;

Step 31: at a suitable temperature such as for example from 50 ºC to 55 ºC, in the presence of a suitable base such as for example K_2HPO_4, in a suitable solvent such as for example H_2O;

Step 32: at a suitable temperature such as for example from -5 °C to 45 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.27 to 0.40 MPa, in the presence of palladium hydroxide on carbon, in the presence of MSA in a suitable solvent such as EtOH;

Step 33: at a suitable temperature such as for example from -50 °C to -40 °C, in the presence of suitable base such as for example TEA, in a suitable solvent such as 2-methyltetrahydrofuran;

Step 34: at a suitable temperature such as for example from 20 °C to 30 °C, in the presence of suitable base such as for example TMG, in a suitable solvent such as 2-methyltetrahydrofuran;
Step 35: at a suitable temperature such as for example from 20 °C to 30 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.20 to 0.30 Mpa, in the presence of a suitable catalyst such as for example palladium on carbon, in a suitable solvent such as MeOH.