57, 1543-1556 describes hydroxy- and aminomethylpiperidine derivatives; *Future Med Chem* 2014, *6*, 447-462 reviews small molecule and peptidomimetic compounds; WO2016195776 describes furo[2,3-d]pyrimidine, 9H-purine, [1,3]oxazolo[5,4-d]pyrimidine, [1,3]oxazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-d]pyrimidine, thieno[2,3-b]pyridine and thieno[2,3-d]pyrimidine derivatives; WO2016197027 describes 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine, 5,6,7,8-tetrahydropyrido]4,3-d]pyrimidine, pyrido[2,3-d]pyrimidine and quinoline derivatives; and WO2016040330 describes thienopyrimidine and thienopyridine compounds. WO2017192543 describes piperidines as Menin inhibitors. WO2017112768, WO2017207387, WO2017214367, WO2018053267 and WO2018024602 describe inhibitors of the menin-MLL interaction. WO2017161002 and WO2017161028 describe inhibitors of menin-MLL. WO2018050686, WO2018050684 and WO2018109088 describe inhibitors of the menin-MLL interaction. WO2018226976 describes methods and compositions for inhibiting the interaction of menin with MLL proteins. WO2018175746 provides methods of treatment for hematological malignancies and Ewing's sarcoma. WO2018106818 and WO2018106820 provide methods of promoting proliferation of a pancreatic cell. WO2018153312 discloses azaspiro compounds relating to the field of medicinal chemistry. WO2017132398 discloses methods comprising contacting a leukemia cell exhibiting an NPM1 mutation with a pharmacologic inhibitor of interaction between MLL and Menin. WO2019060365 describes substituted inhibitors of menin-MLL. WO2020069027 describes the treatment of hematological malignancies with inhibitors of menin. Krivtsov et al., Cancer Cell 2019. No.6 Vol.36, 660-673 describes a menin-MLL inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1: Efficacy study in Molm-14 subcutaneous (sc) model.

Fig. 2: Efficacy study in disseminated OCI-AML3 model.

DESCRIPTION OF THE INVENTION

The present disclosure concerns novel compounds of Formula (I),

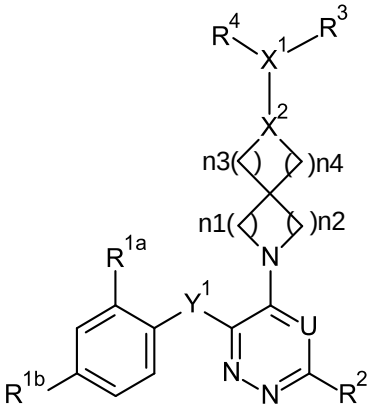
other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

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;

and the pharmaceutically acceptable salts and the solvates thereof.

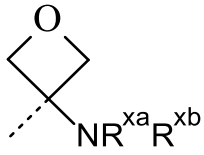
The present disclosure, in one aspect, relates to a compound of Formula (I)



(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.

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), and 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), and myeloproliferative neoplasms (MPN).

In an example, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have improved metabolic stability properties.
In an example, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have extended in vivo half-life (T1/2).
In an example, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have improved oral bioavailability.
In an example, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may reduce tumor growth e.g., tumours harbouring MLL (KMT2A) gene rearrangements/alterations and/or NPM1 mutations.
In an example, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have improved PD properties *in vivo* during a prolonged period of time, e.g. inhibition of target gene expression such as MEIS1 and upregulation of differentiation marker over a period of at least 16 hours.
In an example, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have an improved safety profile (e.g. reduced hERG inhibition; improved cardiovascular safety).
In an example, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may be suitable for Q.D. dosing (once daily).

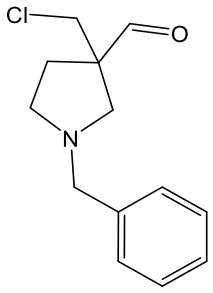
The disclosure also relates to the use of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, in combination with an additional pharmaceutical agent for use in the treatment or prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

Furthermore, the disclosure relates to a process for preparing a pharmaceutical composition according to the disclosure, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof. The present disclosure, in another aspect, relates to a process for preparing a pharmaceutical composition as defined herein comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound as defined herein.

The disclosure also relates to a product comprising a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

Additionally, the disclosure relates to a method of treating or preventing a cell proliferative disease in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, as defined herein, or a pharmaceutical composition or combination as defined herein.

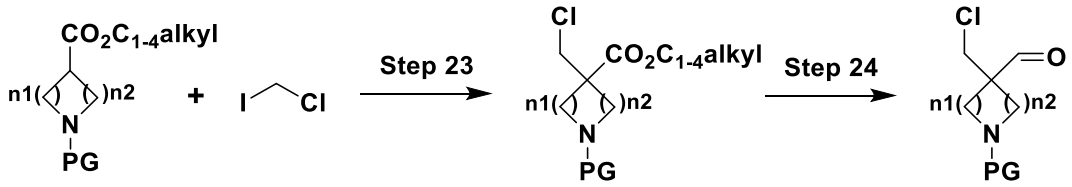
The present disclosure, in another aspect, relates to an intermediate with the structure



or a tautomer or a stereoisomeric form thereof;

or a pharmaceutically acceptable addition salt or a solvate thereof.

The present disclosure, in another aspect, relates to a process for the preparation of an intermediate comprising the following steps:



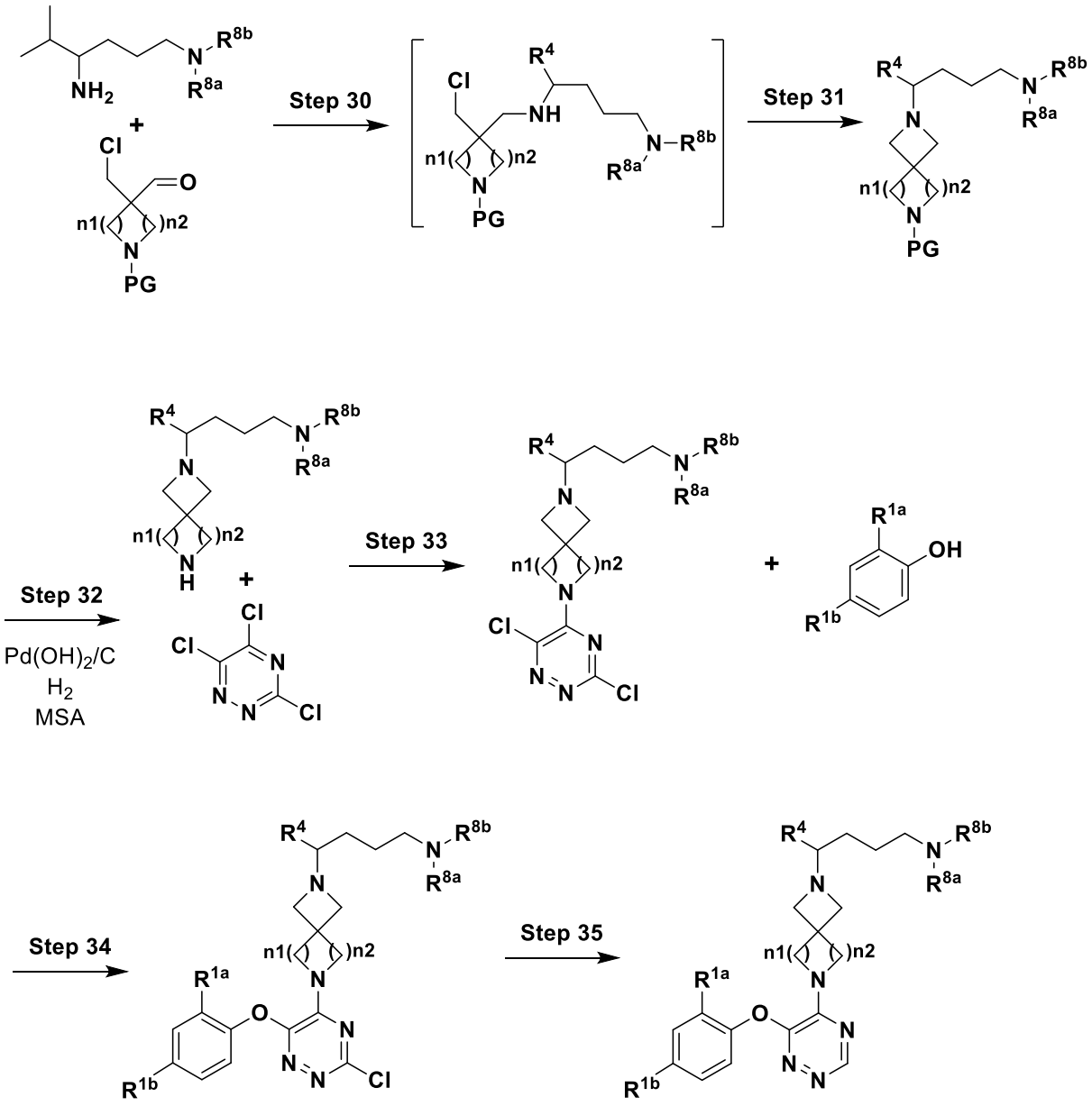
wherein PG is a suitable protecting group such as benzyl;

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

Step 23: at a suitable temperature such as for example from -78 ºC to -25 ºC, 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 ºC, 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.

The present disclosure, in another aspect, relates to 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.