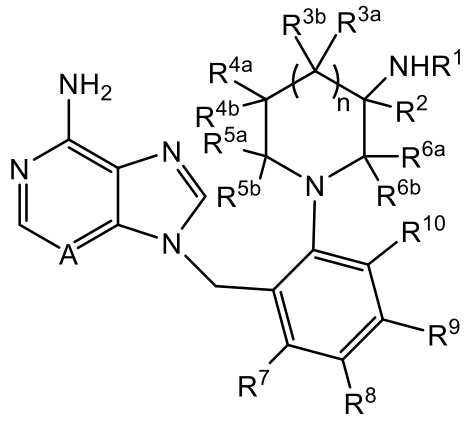
CLAIMS

1. A compound of Formula (I)



(I)

or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein:

A is N or CR wherein R is hydrogen or halo;

R^1 is H; or

R^1 and R^2 together with NH forms a 5-8 membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S as ring members; wherein said 5-8 membered heterocyclyl is unsubstituted or substituted by an oxo substituent;

R^2 is selected from the group consisting of:

(i) -C_{1-6} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkyl, -C_{1-6}alkoxyC_{1-6}alkyl or -C_{3-8} cycloalkoxy(C_{1-6} alkyl);

(ii) cyano, -cyanoC_{1-6} alkyl, -C_{1-6} alkylthioC_{1-6}alkyl, -C_{2-6} alkenyl, -haloC_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{1-4} alkyl-S-C_{1-4}alkyl, -C_{1-4} alkylSO_2C_{1-4}alkyl, -SO_2($_{1-4}$ alkyl) or -C(C_{1-4} alkyl)=N-O(C_{1-4} alkyl);

(iii) -C_{1-4}alkylcarbonyl, -$(CR^aR^b)_p$-C(=O)-OR^{10a} or -C(=O)-$(CR^aR^b)_qR^{11}$;

wherein R^{11} is C_{3-7} cycloalkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, each of which is independently unsubstituted or substituted with -C_{1-6} alkyl or -C_{1-6} alkoxy; and said 5-6 membered heterocyclyl or 5-6 membered heteroaryl independently comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur;

(iv) -$(CR^aR^b)_r$-C(=O)-$NR^{12}R^{13}$ -$(CR^aR^b)_s$-$NR^{12}R^{13}$, -$(CR^aR^b)_{1-4}$-O-$(CR^aR^b)_{1-4}$-OR^{10a} or -$(CR^aR^b)_{1-4}$-O-$(CR^aR^b)_{1-4}$-C(=O)-$NR^{12}R^{13}$;

wherein R^{12} is hydrogen or -C_{1-6} alkyl;

R^{13} is hydrogen, -C_{1-6} alkyl, -C_{1-6}alkoxyC_{1-6}alkyl, -cyanoC_{1-6} alkyl;

-C_{1-4} alkylSO_2R^{10b} wherein R^{10b} is C_{1-6} alkyl or phenyl; C_{3-10} monocylic or bicyclic cycloalkylC_{0-6}alkyl, phenyl, 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroarylC_{0-6}alkyl;

said 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroaryl radical independently comprises 1-4 heteroatoms selected from nitrogen, oxygen and sulfur; and

said C_{3-10} monocylic or bicyclic cycloalkyl, phenyl, 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroaryl radical are independently unsubstituted or substituted with 1-2 -C_{1-4} alkyl, -hydroxyC_{1-6} alkyl, -C_{1-4} alkoxy, halo, hydroxyl, phenyl or -S(C_{1-4} alkyl);

or R^{12} and R^{13} together form a 5-10 membered monocyclic or bicyclic heterocyclic ring comprising 1-4 heteroatoms selected from nitrogen, oxygen and sulfur; and is unsubstituted or substituted with -C_{1-4} alkyl, hydroxyl, cyano, -cyanoC_{1-6} alkyl, -SO_2 or -C_{2-4}alkenylcarbonyl;

(v) 5-6 membered heterocyclylC_{0-6}alkyl or 5-6 membered heterocyclyl(haloC_{1-4} alkyl) wherein each said heterocyclyl radical is unsubstituted or substituted by oxo; and wherein each said heterocyclyl radical comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; and

(vi) phenyl, 5-9 membered heteroarylC_{0-6}alkyl or 5-9 membered heteroaryl(haloC_{1-4}alkyl), wherein each said phenyl or heteroaryl radical is independently unsubstituted or substituted by

-C_{1-4} alkyl, -haloC_{1-4} alkyl, -hydroxyC_{1-4} alkyl, -C_{1-4} alkoxy, -haloC_{1-4} alkoxy, halo, hydroxy, cyano, oxido, amino, -C_{1-4} alkylamino, -C_{1-4} dialkylamino, -aminocarbonylC_{0-6}alkyl, -C_{1-4}alkylaminocarbonylC_{0-6}alkyl, -diC_{1-4}alkylaminocarbonylC_{0-6}alkyl or C_{3-7} cycloalkyl;

wherein each said heteroaryl radical comprises 1-4 heteroatoms selected from nitrogen, oxygen and sulfur;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a} and R^{6b} are independently hydrogen, halo, cyano, hydroxyl,

-C_{1-6} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkyl, -C_{1-6} alkoxy, -C_{1-6}alkoxyC_{1-6}alkyl, aryl, -C(=O)-OR^{14} or -$(CR^aR^b)_s$-C(=O)-$NR^{15}R^{16}$; or

R^{3a} and R^{3b}, R^{4a} and R^{4b}, R^{5a} and R^{5b} or R^{6a} and R^{6b} forms an oxo substituent;

R^7, R^8, R^9 and R^{10} are independently hydrogen, halo, -C_{1-4} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkyl, cyano, -cyanoC_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{1-6} alkylthio, -$(CR^aR^b)_{1-4}$-$NR^{17}R^{18}$,

-$(CR^aR^b)_{1-4}NR^{17}$-C(O)-OR^{18}, -$(CR^aR^b)_{1-4}$–OR^{19}, C_{3-8} cycloalkyl, phenyl or 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; wherein said C_{3-8} cycloalkyl, phenyl or 5-6 membered heteroaryl is independently substituted with 1-2 R^{20}; and provided at least one of R^7, R^8, R^9 and R^{10} is not hydrogen;

alternatively, R^7 and R^8, R^8 and R^9, and R^9 together with the phenyl ring to which they are attached form a 9-10 membered benzo-fused carbocycle or benzo-fused heterocycle comprising 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; wherein said benzo-fused carbocycle or benzo-fused heterocycle is independently unsubstituted or substituted with 1-2 halo or C_{1-4} alkyl;

R^a, R^b, R^{10a}, R^{14}, R^{15}, R^{16} and R^{17} are independently hydrogen or -C_{1-4} alkyl;

R^{18} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl or -C_{3-6} cycloalkyl;

alternatively, R^{17} and R^{18} together with N in the -$NR^{17}R^{18}$ moiety form a 4-10 membered monocyclic or bicyclic heterocyclic ring comprising 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; wherein said 4-10 membered monocyclic or bicyclic heterocyclic ring is unsubstituted or substituted with 1-2 halo or C_{1-4} alkyl;

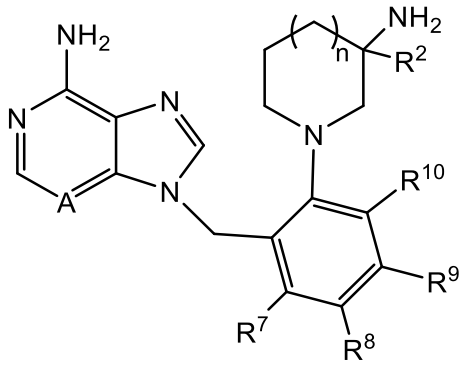
R^{19} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl, -C_{3-6} cycloalkyl, phenyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl; wherein said 5-6 membered heterocyclyl or 5-6 membered heteroaryl independently comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur;

R^{20} is -C_{1-4} alkyl, -halo or -C_{3-6} cycloalkyl; or two R^{20} together form a 5-6 membered ring comprising 0-2 heteroatoms selected from nitrogen, oxygen and sulfur;

n is 0 or 1; and

p, q, r, s and t are independently 0, 1, 2, 3 or 4.

2. The compound of Formula (I) in claim 1, wherein said compound is a compound of Formula (II):



(II)

or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein:

R^2 is selected from the group consisting of:

(i) -hydroxyC_{1-6} alkyl, -C_{1-6}alkoxyC_{1-6}alkyl or -$(CR^aR^b)_p$-C(=O)-OR^{10a};

(ii) -$(CR^aR^b)_r$-C(=O)-$NR^{12}R^{13}$ or -$(CR^aR^b)_{1-4}$-O-$(CR^aR^b)_{1-4}$-C(=O)-$NR^{12}R^{13}$; wherein

R^{12} is hydrogen or -C_{1-6} alkyl;

R^{13} is hydrogen, -C_{1-6} alkyl, -cyanoC_{1-6} alkyl; -C_{1-4} alkylSO_2R^{10b} wherein R^{10b} is -C_{1-6} alkyl or phenyl; C_{3-10} monocylic or bicyclic cycloalkylC_{0-6}alkyl, phenyl, 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroarylC_{0-6}alkyl; wherein said 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroaryl radical independently comprises 1-4 heteroatoms selected from nitrogen, oxygen and sulfur; and

said C_{3-10} monocylic or bicyclic cycloalkyl, phenyl, 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroaryl radical are independently

unsubstituted or substituted with 1-2 -C_{1-4} alkyl, -hydroxyC_{1-6} alkyl, -C_{1-4} alkoxy, halo, hydroxyl, phenyl or -S(C_{1-4} alkyl); or

R^{12} and R^{13} together form a 5-10 membered monocyclic or bicyclic heterocyclic ring comprising 1-4 heteroatoms selected from nitrogen, oxygen and sulfur; and is unsubstituted or substituted with -C_{1-4} alkyl, hydroxyl, cyano, -cyanoC_{1-6} alkyl, -SO_2 or -C_{2-4}alkenylcarbonyl; and

(iii) phenyl or 5-9 membered heteroarylC_{0-6}alkyl; wherein said heteroaryl radical is unsubstituted or substituted by -C_{1-4} alkyl, -haloC_{1-4} alkyl, amino, -C_{1-4} alkylamino or -C_{1-4} dialkylamino; and said heteroaryl radical comprises 1-4 heteroatoms selected from nitrogen, oxygen and sulfur;

R^7, R^8, R^9 and R^{10} are independently hydrogen, halo, -C_{1-4} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkyl, cyano, -cyanoC_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{1-6} alkylthio, -$(CR^aR^b)_{1-4}$-$NR^{17}R^{18}$,
-$(CR^aR^b)_{1-4}NR^{17}$-C(O)-OR^{18}, -$(CR^aR^b)_{1-4}$–OR^{19}, -C_{3-8} cycloalkyl, phenyl or 5-6 membered heteroaryl comprising 1-4 heteroatoms selected from nitrogen, oxygen and sulfur; and

wherein said C_{3-8} cycloalkyl, phenyl or 5-6 membered heteroaryl is independently substituted with 1-2 R^{20}; and

provided at least one of R^7, R^8, R^9 and R^{10} is not hydrogen;

alternatively, R^7 and R^8, R^8 and R^9, R^9 and R^{10} together with the phenyl ring to which they are attached form a 9-10 membered benzo-fused carbocycle or benzo-fused heterocycle comprising 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; wherein said benzo-fused carbocycle or benzo-fused heterocycle is independently unsubstituted or substituted with 1-2 halo or -C_{1-4} alkyl;

R^a, R^b, R^{10a} and R^{17} are independently hydrogen or -C_{1-4} alkyl;

R^{18} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl or -C_{3-6} cycloalkyl;

alternatively, R^{17} and R^{18} together with N in the -$NR^{17}R^{18}$ moiety form a 4-10 membered monocyclic or bicyclic heterocyclic ring comprising 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; wherein said heterocyclic ring is unsubstituted or substituted with 1-2 halo or -C_{1-4} alkyl;

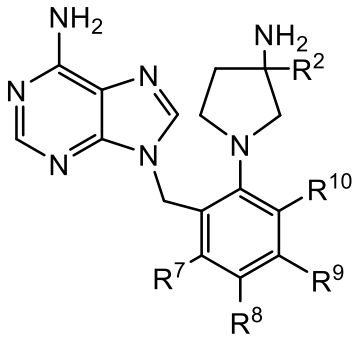
R^{19} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl, -C_{3-6} cycloalkyl, phenyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl; wherein said 5-6 membered heterocyclyl or 5-6 membered heteroaryl independently comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur;

R^{20} is -C_{1-4} alkyl, halo or -C_{3-6} cycloalkyl; or two R^{20} together form a 5-6 membered ring comprising 0-2 heteroatoms selected from nitrogen, oxygen and sulfur;

n is 0 or 1; and

p, q, r, s and t are independently 0, 1, 2, 3 or 4.

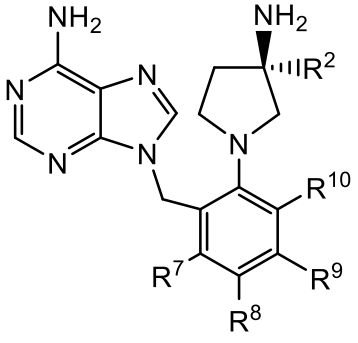
3. The compound of Formula (II) in claim 2, wherein said compound is a compound of Formula (III):



(III)

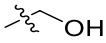
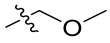
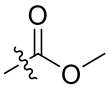
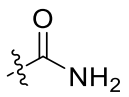
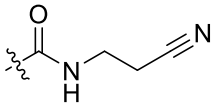
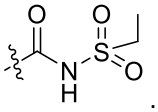
or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof.

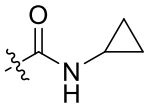
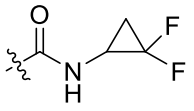
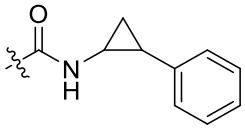
4. The compound of Formula (III) in claim 3, wherein said compound is a compound of Formula (IV):

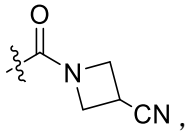


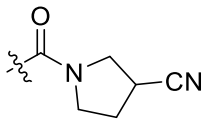
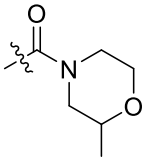
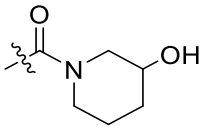
(IV)

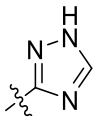
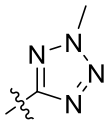
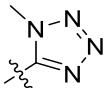
or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^2 is , , , ,  or .

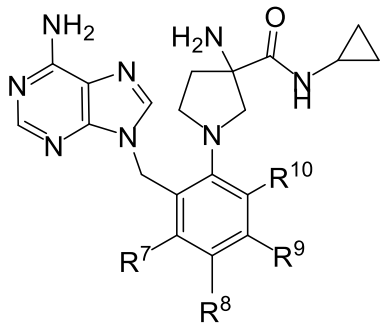
6. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^2 is, ,  or .

7. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^2 is ,

,  or .

8. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^2 is , , , 1H-tetrazolyl, 2H-tetrazoly, pyridyl, trifluoromethylpyridyl or phenyl.

9. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein said compound is a compound of Formula (V):



(V)

10. The compound of any one of claims 1-9 or a pharmaceutically acceptable salt thereof; wherein at least two of R^7, R^8, R^9 and R^{10} are not hydrogen.

11. The compound of claim 10 or a pharmaceutically acceptable salt thereof; wherein R^7, R^8, R^9 and R^{10} are independently hydrogen, halo, -C_{1-4}alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkyl, -C_{2-6} alkenyl, -C_{3-8} cycloalkyl, -$(CR^aR^b)_{1-4}$-$NR^{17}R^{18}$, or -$(CR^aR^b)_{1-4}$–OR^{19}; provided at least two of R^7, R^8, R^9 and R^{10} are not hydrogen;

R^a, R^b and R^{17} are independently hydrogen or -C_{1-4} alkyl;

R^{18} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl or -C_{3-6} cycloalkyl;

alternatively, R^{17} and R^{18} together with N in the -$NR^{17}R^{18}$ moiety form a 4-10 membered monocyclic or bicyclic heterocyclic ring comprising 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; wherein said heterocyclic ring is unsubstituted or substituted with 1-2 halo or -C_{1-4} alkyl; and

R^{19} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl, -C_{3-6} cycloalkyl, phenyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl; wherein said 5-6 membered heterocyclyl or 5-6 membered heteroaryl independently comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur.

12. The compound according to claim 1 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein said compound is selected from a compound in Table 2, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier.

14. A combination comprising a compound according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agent.

15. The combination according to claim 14, wherein said one or more therapeutically active agent is an anti-cancer agent, an analgesic or an anti-inflammatory agent.

16. Use of a compound according to any of claims 1-12 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament ~~A method~~ for treating a disease or condition that benefit from or is treatable by inhibition of mixed lineage leukemia 1 (MLL1)~~, comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound according to any of claims 1-12 or a pharmaceutically acceptable salt thereof~~.

17. The ~~method~~use of claim 16, wherein said disease or condition that benefit from or is treatable by inhibition of MLL1 is selected from solid tumors, leukemia, myeloma, lymphoma and hypertension.

18. The ~~method~~use of claim 16, wherein said disease or condition that benefit from or is treatable by inhibition of MLL1 is breast cancer, cervical cancer, skin cancer, ovarian cancer, gastric cancer, prostate cancer, pancreatic cancer, lung cancer, hepatocellular carcinoma, head and neck cancer, peripheral nerve sheath tumor, osteosarcoma, multiple myeloma, neuroblastoma, leukemia, non-Hodgkin's lymphoma or pulmonary arterial hypertension.

19. The ~~method~~use of claim 18, wherein said disease or condition that benefit from or is treatable by inhibition of MLL1 is leukemia, skin cancer or lymphoma; wherein

said leukemia is acute lymphoblastic leukemia;

said skin cancer is skin squamous cell carcinoma; and

said lymphoma is mantle cell lymphoma.

~~20. Use of a compound according to any one of claims 1-18 and optionally in combination with a second therapeutic agent, in the manufacture of a medicament for a disease or condition that benefit from or is treatable by inhibition of mixed lineage leukemia 1 (MLL1).~~