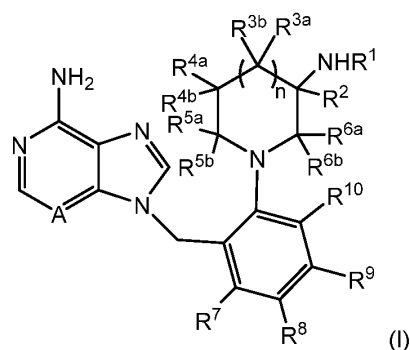


CLAIMS

1. A compound of Formula (I)



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

5 wherein:

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

R¹ is H; or

R¹ and R² 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

10 unsubstituted or substituted by an oxo substituent;

R² is selected from the group consisting of:

(i) -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkyl, -C₁₋₆alkoxyC₁₋₆alkyl or -C₃₋₈ cycloalkoxy(C₁₋₆ alkyl);

(ii) cyano, -cyanoC₁₋₆ alkyl, -C₁₋₆ alkylthioC₁₋₆alkyl, -C₂₋₆ alkenyl, -haloC₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₁₋₄ alkyl-S-C₁₋₄alkyl, -C₁₋₄ alkylSO₂C₁₋₄alkyl, -SO₂(C₁₋₄ alkyl) or -C(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl);

(iii) -C₁₋₄alkylcarbonyl, -(CR^aR^b)_p-C(=O)-OR^{10a} or -C(=O)-(CR^aR^b)_qR¹¹;

wherein R¹¹ is C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, each of which is independently unsubstituted or substituted with -C₁₋₆ alkyl or -C₁₋₆ 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)-NR¹²R¹³ -(CR^aR^b)_s-NR¹²R¹³, -(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)-NR¹²R¹³;

wherein R¹² is hydrogen or -C₁₋₆ alkyl;

R¹³ is hydrogen, -C₁₋₆ alkyl, -C₁₋₆alkoxyC₁₋₆alkyl, -cyanoC₁₋₆ alkyl;

-C₁₋₄ alkylSO₂R^{10b} wherein R^{10b} is C₁₋₆ alkyl or phenyl; C₃₋₁₀ monocyclic or bicyclic cycloalkylC₀₋₆alkyl, phenyl, 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroarylC₀₋₆alkyl;

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

5 said C₃₋₁₀ monocyclic 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 -C₁₋₄ alkyl, -hydroxyC₁₋₆ alkyl, -C₁₋₄ alkoxy, halo, hydroxyl, phenyl or -S(C₁₋₄ alkyl);

or R¹² and R¹³ 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 -C₁₋₄ alkyl, hydroxyl, cyano, -cyanoC₁₋₆ alkyl, -SO₂ or -C₂₋₄ alkenylcarbonyl;

(v) 5-6 membered heterocyclylC₀₋₆alkyl or 5-6 membered heterocyclyl(haloC₁₋₄alkyl) 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 heteroarylC₀₋₆alkyl or 5-9 membered heteroaryl(haloC₁₋₄alkyl), wherein each said phenyl or heteroaryl radical is independently unsubstituted or substituted by -C₁₋₄ alkyl, -haloC₁₋₄ alkyl, -hydroxyC₁₋₄ alkyl, -C₁₋₄ alkoxy, -haloC₁₋₄ alkoxy, halo, hydroxy, cyano, oxido, amino, -C₁₋₄ alkylamino, -C₁₋₄ dialkylamino, -aminocarbonylC₀₋₆alkyl, -C₁₋₄alkylaminocarbonylC₀₋₆alkyl, -diC₁₋₄alkylaminocarbonylC₀₋₆alkyl or C₃₋₇ 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, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkyl, -C₁₋₆ alkoxy, -C₁₋₆alkoxyC₁₋₆alkyl, aryl, -C(=O)-OR¹⁴ or -(CR^aR^b)_s-C(=O)-NR¹⁵R¹⁶; 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;

R⁷, R⁸, R⁹ and R¹⁰ are independently hydrogen, halo, -C₁₋₄ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkyl, cyano, -cyanoC₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₁₋₆ alkylthio, -(CR^aR^b)₁₋₄-NR¹⁷R¹⁸, -(CR^aR^b)₁₋₄NR¹⁷-C(O)-OR¹⁸, -(CR^aR^b)₁₋₄-OR¹⁹, C₃₋₈ cycloalkyl, phenyl or 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from nitrogen, oxygen and sulfur; wherein said C₃₋₈ cycloalkyl, phenyl or 5-6 membered heteroaryl is independently substituted with 1-2 R²⁰; and provided at least one of R⁷, R⁸, R⁹ and R¹⁰ is not hydrogen;

alternatively, R⁷ and R⁸, R⁸ and R⁹, and R⁹ 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 C₁₋₄ alkyl;

R^a, R^b, R^{10a}, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are independently hydrogen or -C₁₋₄ 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
5 unsubstituted or substituted with 1-2 halo or C_{1-4} alkyl;

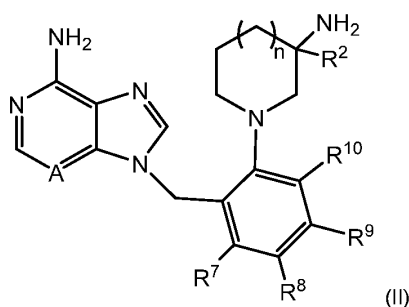
R^{19} is hydrogen, $-C_{1-4}$ alkyl, $-haloC_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, phenyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl; wherein said 5-6 membered heterocyclyl or 5-6 membered heteroaryl independently comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur;

10 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
15 Formula (II):



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

20 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; $-C_{1-4}$ alkyl SO_2R^{10b} wherein R^{10b} is $-C_{1-6}$ alkyl
25 or phenyl; C_{3-10} monocyclic or bicyclic cycloalkyl $C_{0-6}alkyl$, phenyl, 5-10 membered monocyclic or bicyclic heterocyclic ring or 5-9 membered heteroaryl $C_{0-6}alkyl$; 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} monocyclic or bicyclic cycloalkyl, phenyl, 5-10 membered monocyclic or
30 bicyclic heterocyclic ring or 5-9 membered heteroaryl radical are independently

unsubstituted or substituted with 1-2 -C₁₋₄ alkyl, -hydroxyC₁₋₆ alkyl, -C₁₋₄ alkoxy, halo, hydroxyl, phenyl or -S(C₁₋₄ alkyl); or

R¹² and R¹³ 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 -C₁₋₄ alkyl, hydroxyl, cyano, -cyanoC₁₋₆ alkyl, -SO₂ or -C₂₋₄ alkenylcarbonyl; and (iii) phenyl or 5-9 membered heteroarylC₀₋₆alkyl; wherein said heteroaryl radical is unsubstituted or substituted by -C₁₋₄ alkyl, -haloC₁₋₄ alkyl, amino, -C₁₋₄ alkylamino or -C₁₋₄ dialkylamino; and said heteroaryl radical comprises 1-4 heteroatoms selected from nitrogen, oxygen and sulfur;

R⁷, R⁸, R⁹ and R¹⁰ are independently hydrogen, halo, -C₁₋₄ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkyl, cyano, -cyanoC₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₁₋₆ alkylthio, -(CR^aR^b)₁₋₄-NR¹⁷R¹⁸, -(CR^aR^b)₁₋₄NR¹⁷-C(O)-OR¹⁸, -(CR^aR^b)₁₋₄-OR¹⁹, -C₃₋₈ cycloalkyl, phenyl or 5-6 membered heteroaryl comprising 1-4 heteroatoms selected from nitrogen, oxygen and sulfur; and

wherein said C₃₋₈ cycloalkyl, phenyl or 5-6 membered heteroaryl is independently substituted with 1-2 R²⁰; and

provided at least one of R⁷, R⁸, R⁹ and R¹⁰ is not hydrogen;

alternatively, R⁷ and R⁸, R⁸ and R⁹, R⁹ and R¹⁰ 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 -C₁₋₄ alkyl;

R^a, R^b, R^{10a} and R¹⁷ are independently hydrogen or -C₁₋₄ alkyl;

R¹⁸ is hydrogen, -C₁₋₄ alkyl, -haloC₁₋₆ alkyl or -C₃₋₆ cycloalkyl;

alternatively, R¹⁷ and R¹⁸ together with N in the -NR¹⁷R¹⁸ 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 -C₁₋₄ alkyl;

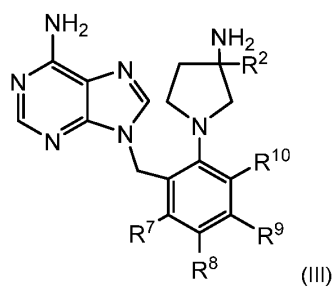
R¹⁹ is hydrogen, -C₁₋₄ alkyl, -haloC₁₋₆ alkyl, -C₃₋₆ cycloalkyl, phenyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl; wherein said 5-6 membered heterocyclyl or 5-6 membered heteroaryl independently comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur;

R²⁰ is -C₁₋₄ alkyl, halo or -C₃₋₆ cycloalkyl; or two R²⁰ together form a 5-6 membered ring comprising 0-2 heteroatoms selected from nitrogen, oxygen and sulfur;

n is 0 or 1; and

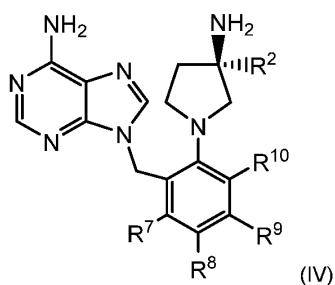
p, q, r, s and t are independently 0, 1, 2, 3 or 4.

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



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

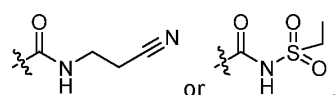
4. The compound of Formula (III) in claim 3, wherein said compound is a compound of Formula (IV):



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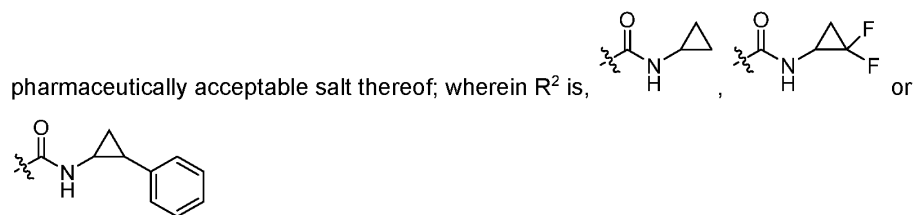
or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R² is , , , ,

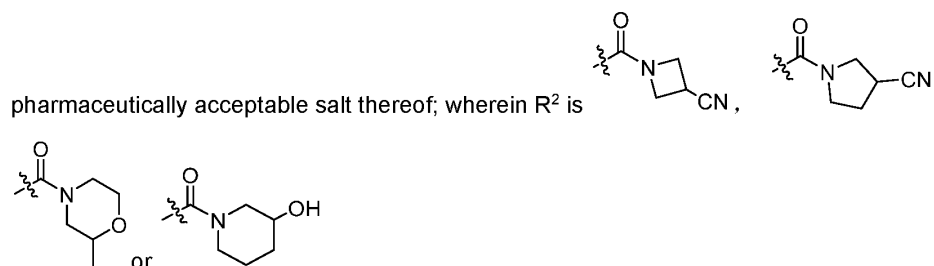


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6. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a



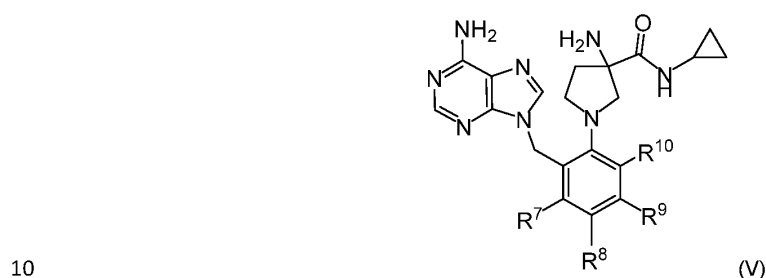
7. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a



8. The compound of any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a

5 pharmaceutically acceptable salt thereof; wherein R^2 is , 1H-tetrazolyl, 2H-tetrazolyl, 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):



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, $-\text{halo}C_{1-6}$ alkyl, $-\text{hydroxy}C_{1-6}$ 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, $-\text{halo}C_{1-6}$ 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

20

R¹⁹ is hydrogen, -C₁₋₄ alkyl, -haloC₁₋₆ alkyl, -C₃₋₆ 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.

5 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.

10 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 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. 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.

20 17. The method 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.

25 18. The method 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.

30 19. The method 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).