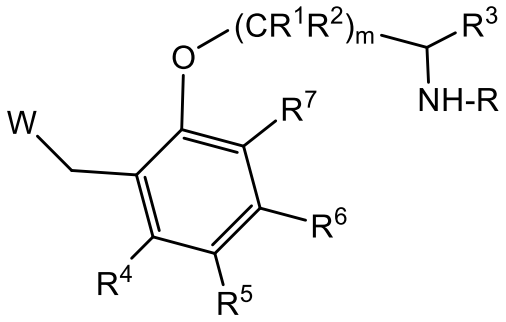
	(*R*)-2-amino-5-(2-((4-aminopyrazolo[1,5-*a*][1,3,5]triazin-8-yl)methyl)-3,4-dichlorophen oxy)pentan-1-ol	+	+	-	+
26	(R)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-dichlorophenoxy)pentan-1-ol	++	-	++	++
27	1-(2-(4-aminobutoxy)-4,6-dichlorobenzyl)-1H-imidazo[4,5-c]pyridin-4-amine	+	-	-	-
28	(R)-9-(6-((4-amino-5-(2-methoxyethoxy)pentyl)oxy)-2,3-dichlorobenzyl)-9H-purin-6-amine	+	-	+	+
29	(R)-9-(6-(4-amino-4-(1H-1,2,4-triazol-3-yl)butoxy)-2,3-dichlorobenzyl)-9H-purin-6-amine	+++	+++	+++	+++
30	(R)-9-(6-((4-amino-5-(1H-pyrazol-1-yl)pentyl)oxy)-2,3-dichlorobenzyl)-9H-purin-6-amine	++	-	+	-
31	(*R*)-9-(6-(4-amino-4-(5-methyl-1,3,4-thiadiazol-2-yl)butoxy)-2,3-dichlorobenzyl)-9*H*-purin-6-amine	+++	+	+	+++
32	(R)-9-(6-(4-amino-4-(1,3,4-oxadiazol-2-yl)butoxy)-2,3-dichlorobenzyl)-9H-purin-6-amine	+	-	+	++
33	(*R*)-9-(6-((4-amino-5-(methylthio)pentyl)oxy)-2,3-dichlorobenzyl)-9*H*-purin-6-amine	++	-	+	+
34	(*R*)-5-(2-((6-amino-9*H*-purin-9-yl)methyl)-3,4-dichlorophenoxy)-N^1,N^1-dimethylpentane-1,2-diamine	+	+	+	+

Legend:	"+++"	"++"	"+"
LCMS	<0.05 μM	0.05-0.10 μM	>0.10 μM
MLL1 flash plate	<0.06 μM	0.06-0.10 μM	>0.10 μM
ELISA	<1.9 μM	1.9-3.0 μM	>3.0 μM
CTG MV4:11	<2.0 μM	2.0-3.0 μM	>3.0 μM

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

CLAIMS

1. A compound of Formula (I)

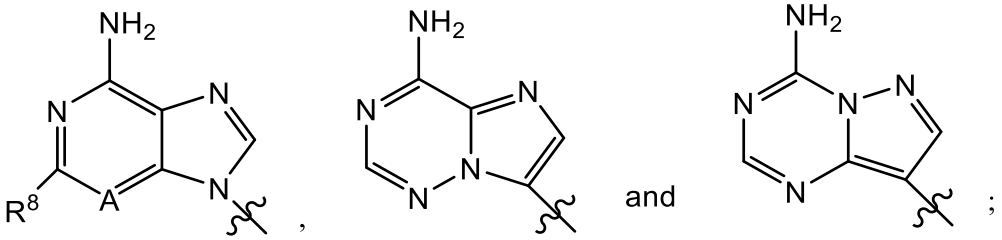


(I)

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

wherein:

W is selected from:



A is N or CR^9 wherein R^9 is hydrogen or halo;

R, R^1 and R^2 are independently H or C_{1-4} alkyl;

R^3 is hydrogen or 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, -C_{3-8} cycloalkoxy(C_{1-6} alkyl), 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(C_{1-4} alkyl), or -C(C_{1-4} alkyl)=N-O(C_{1-4} alkyl);

(ii) -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;

(iii) -$(CR^aR^b)_r$-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_{0-4} alkylSO_2R^{10b} wherein R^{10b} is -C_{1-6} alkyl or phenyl; C_{3-10} monocyclic 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} 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 -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 with 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^4, R^5, R^6 and R^7 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, -$(CR^aR^b)_{1-4}$-$NR^{14}R^{15}$, -$(CR^aR^b)_{1-4}NR^{14}$-C(O)-OR^{15}, -$(CR^aR^b)_{1-4}$-OR^{16}, 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^{17};

alternatively, R^4 and R^5, R^5 and R^6, and R^6 and R^7 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^8 is hydrogen, -C_{1-4} alkyl or -C_{1-4} alkoxy;

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

R^{15} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl or -C_{3-6} cycloalkyl;

alternatively, R^{14} and R^{15} together with N in the -$NR^{14}R^{15}$ 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;

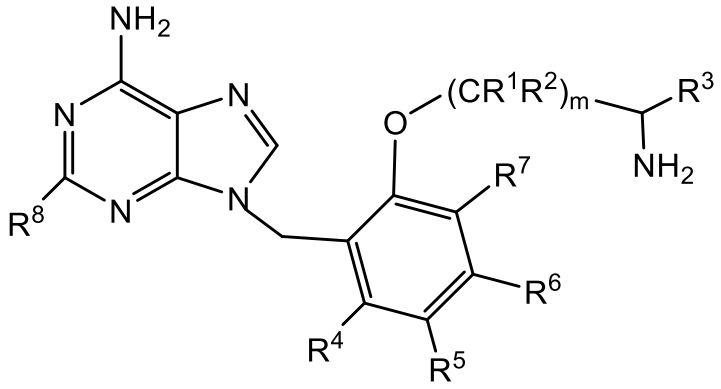
R^{16} is hydrogen, -C_{1-4} alkyl, -haloC_{1-6} alkyl, -C_{3-6} cycloalkyl, phenyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl; wherein said 5-6 membered heterocyclyl or 5-6 membered heteroaryl independently comprises 1-3 heteroatoms selected from nitrogen, oxygen and sulfur;

R^{17} is -C_{1-4} alkyl, halo or -C_{3-6} cycloalkyl; or two R^{20} together form a 5-6 membered ring;

m is 1, 2, 3 or 4; and

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

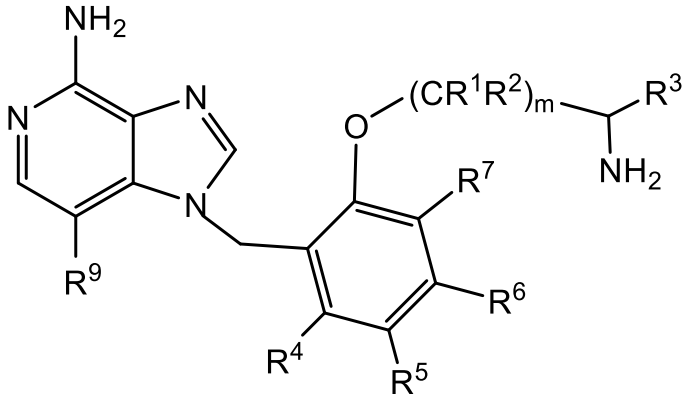
2. The compound of Formula (I) in claim 1, wherein said compound is of Formula (II):



(II)

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

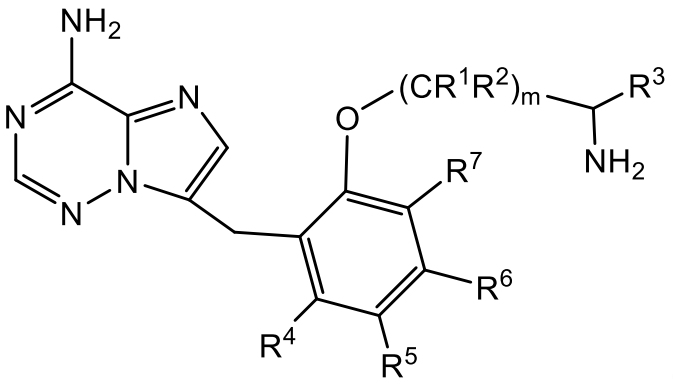
3. The compound of Formula (I) in claim 1, wherein said compound is of Formula (III):



(III)

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

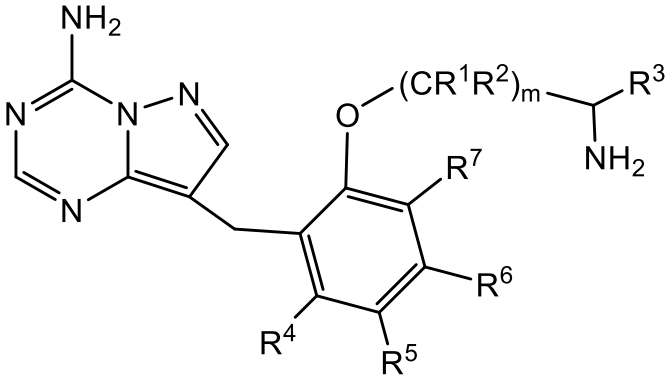
4. The compound of Formula (I) in claim 1, wherein said compound is of Formula (IV):



(IV)

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

5. The compound of Formula (I) in claim 1, wherein said compound is of Formula (V):



(V)

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

6. The compound according to any one of claims 1-5, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^3 is hydrogen, -hydroxyC_{1-6}alkyl, -C_{1-6}alkoxyC_{1-6}alkyl, -C_{1-4}alkyl-S-C_{1-4}alkyl, -C(=O)-OR^{10a}, -C(=O)-$NR^{12}R^{13}$, -(CR^aR^b)-$NR^{12}R^{13}$, -(CR^aR^b)-O-(CR^aR^b)$_2$-O-C_{1-6}alkyl or 5-9 membered heteroarylC_{0-6}alkyl wherein said heteroaryl radical is unsubstituted or substituted by -C_{1-4} alkyl;

wherein R^a, R^b, R^{10a} and R^{12} are independently hydrogen or C_{1-4} alkyl;

R^{13} is hydrogen, -C_{1-6} alkyl, -C_{1-6}alkoxyC_{1-6}alkyl, -SO_2-(C_{1-4} alkyl) or -cyclopropyl; and

m is 1, 2, 3 or 4.

7. The compound according to any one of claims 1-5, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^3 is -C_{1-6}alkoxyC_{1-6}alkyl, -C(=O)-OR^{10a}, -C(=O)-$NR^{12}R^{13}$, triazolyl or thiadiazolyl unsubstituted or substituted by -C_{1-4} alkyl;

wherein R^a, R^b, R^{10a} and R^{12} are independently hydrogen or C_{1-4} alkyl;

R^{13} is hydrogen, -C_{1-6}alkoxyC_{1-6}alkyl, -SO_2-(C_{1-4} alkyl) or -cyclopropyl; and

m is 1, 2 or 3.

8. The compound according to any one of claims 1-7, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein:

R^4 and R^5 are halo; and

R^6 and R^7 are hydrogen.

9. The compound according to any one of claims 1-7, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein:

R^4 is halo or -C_{1-4} alkyl;

R^6 is halo; and

R^5 and R^7 are hydrogen.

10. The compound according to any one of claims 1-7, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^4 and R^5 together with the phenyl ring to which they are attached form a 9-10 membered benzo-fused carbocycle; wherein said benzo-fused carbocycle is unsubstituted or substituted with halo; and

R^6 and R^7 are hydrogen.

11. The compound according to any one of claims 1-7, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein:

R^4 and R^7 are hydrogen; and

R^5 and R^6 together with the phenyl ring to which they are attached form a 9-10 membered benzo-fused carbocycle.

12. The compound according to any one of claims 1-7, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^4, R^5, R^6 and R^7 are hydrogen; or wherein one of R^4, R^5, R^6 and R^7 is halo and the others are hydrogen.

13. The compound according to claim 1, wherein said compound is selected from:

(*R*)-9-(6-((4-amino-5-methoxypentyl)oxy)-2,3-dichlorobenzyl)-9*H*-purin-6-amine;

(*R*)-9-(2-(3-amino-4-methoxybutoxy)-6-bromo-4-chlorobenzyl)-9H-purin-6-amine;

(*S*)-9-(2-(3-amino-4-methoxybutoxy)-4-chloro-6-methylbenzyl)-9H-purin-6-amine;

(S)-9-(2-(3-amino-4-methoxybutoxy)-4-chloro-6-ethylbenzyl)-9H-purin-6-amine;

(*R*)-7-(6-((4-amino-5-methoxypentyl)oxy)-2,3-dichlorobenzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine;

(*R*)-7-(2-((4-amino-5-methoxypentyl)oxy)-6-chlorobenzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine;

(*R*)-7-(2-((4-amino-5-methoxypentyl)oxy)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine;

(*R*)-8-(6-((4-amino-5-methoxypentyl)oxy)-2,3-dichlorobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-8-(2-((4-amino-5-methoxypentyl)oxy)-6-bromo-4-chlorobenzyl)pyrazolo[1,5-*a*][1,3,5] triazin-4-amine;

(*R*)-8-(2-((4-amino-5-methoxypentyl)oxy)-6-bromobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-8-(2-((4-amino-5-methoxypentyl)oxy)-6-chlorobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-8-(2-((4-amino-5-methoxypentyl)oxy)benzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-8-(2-((4-amino-5-methoxypentyl)oxy)-4-chlorobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-8-(2-((4-amino-5-methoxypentyl)oxy)-3-chlorobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-8-(6-((4-amino-5-isobutoxypentyl)oxy)-2,3-dichlorobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-8-(6-((4-amino-5-ethoxypentyl)oxy)-2,3-dichlorobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*S*)-8-(6-(3-amino-4-methoxybutoxy)-2,3-dichlorobenzyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine;

(*R*)-1-(6-((4-amino-5-methoxypentyl)oxy)-2,3-dichlorobenzyl)-7-chloro-1*H*-imidazo[4,5-c]pyridin-4-amine;

(*S*)-9-((2-(2-amino-3-methoxypropoxy)naphthalen-1-yl)methyl)-9*H*-purin-6-amine;

(*R*)-9-((2-((4-amino-5-methoxypentyl)oxy)-6-bromonaphthalen-1-yl)methyl)-9H-purin-6-amine;

(R)-9-((3-((4-amino-5-methoxypentyl)oxy)naphthalen-2-yl)methyl)-9H-purin-6-amine;

(*R*)-9-(2-bromo-4-chloro-6-((5-methoxy-4-(methylamino)pentyl)oxy)benzyl)-9H-purin-6-amine;

(*R*)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-dichlorophenoxy)pentanoic acid;

(*R*)-2-amino-5-(2-((4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)methyl)-3,4-dichlorophenoxy) pentanoic acid;

O-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-difluorophenyl)-L-homoserine;

(*R*)-2-amino-5-(2-((6-amino-2-isopropyl-9H-purin-9-yl)methyl)-3,5-dichlorophenoxy)pentanoic acid;

(*R*)-2-amino-5-(2-((6-amino-2-methoxy-9*H*-purin-9-yl)methyl)-3,5-dichlorophenoxy)pentanoic acid;

2-amino-5-(2-((4-amino-7-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)methyl)-3,5-dichlorophenoxy) pentanoic acid;

Ethyl (*R*)-2-amino-5-(2-((6-amino-9*H*-purin-9-yl)methyl)-3,4-dichlorophenoxy)pentanoate;

Ethyl (2*R*)-2-amino-5-(2-((6-amino-9*H*-purin-9-yl)methyl)-3,4-dichlorophenoxy)hexanoate;

Methyl 2-amino-5-(2-((4-amino-7-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)methyl)-3,5-dichloro phenoxy)pentanoate;

Ethyl (*R*)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,5-dichlorophenoxy)pentanoate;

Methyl (*R*)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-dichlorophenoxy)pentanoate;

Methyl (*R*)-2-amino-5-(2-((4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)methyl)-3,4-dichlorophenoxy)pentanoate;

(*R*)-2-amino-5-(2-((4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)methyl)-3,4-dichlorophenoxy)pentanamide;

(*R*)-2-amino-5-(2-((4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)methyl)-3,4-dichlorophenoxy)-*N*-cyclopropylpentanamide;

(*R*)-2-amino-5-(2-((4-aminopyrazolo[1,5-*a*][1,3,5]triazin-8-yl)methyl)-3,4-dichlorophenoxy)-*N*-cyclopropylpentanamide;

(*R*)-2-amino-5-(2-((4-amino-7-chloro-1*H*-imidazo[4,5-c]pyridin-1-yl)methyl)-3,5-dichlorophenoxy)pentanamide;

(*R*)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-dichlorophenoxy)pentanamide;

(*R*)-2-amino-5-(2-((6-amino-9*H*-purin-9-yl)methyl)-3,4-dichlorophenoxy)-*N*-methylpentanamide;

(*R*)-2-amino-5-(2-((6-amino-9*H*-purin-9-yl)methyl)-3,4-dichlorophenoxy)-*N*-(2-methoxyethyl) pentanamide;

(*R*)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-dichlorophenoxy)-N-cyclopropylpentanamide;

(*R*)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-dichlorophenoxy)-N-(methylsulfonyl)pentanamide;

(*R*)-2-amino-5-(2-((4-aminopyrazolo[1,5-*a*][1,3,5]triazin-8-yl)methyl)-3,4-dichlorophenoxy)pentan-1-ol;

(*R*)-2-amino-5-(2-((6-amino-9H-purin-9-yl)methyl)-3,4-dichlorophenoxy)pentan-1-ol;

1-(2-(4-aminobutoxy)-4,6-dichlorobenzyl)-1H-imidazo[4,5-c]pyridin-4-amine;

(*R*)-9-(6-((4-amino-5-(2-methoxyethoxy)pentyl)oxy)-2,3-dichlorobenzyl)-9H-purin-6-amine;

(R)-9-(6-(4-amino-4-(1H-1,2,4-triazol-3-yl)butoxy)-2,3-dichlorobenzyl)-9H-purin-6-amine;

(R)-9-(6-((4-amino-5-(1H-pyrazol-1-yl)pentyl)oxy)-2,3-dichlorobenzyl)-9H-purin-6-amine;

(*R*)-9-(6-(4-amino-4-(5-methyl-1,3,4-thiadiazol-2-yl)butoxy)-2,3-dichlorobenzyl)-9*H*-purin-6-amine;

(*R*)-9-(6-(4-amino-4-(1,3,4-oxadiazol-2-yl)butoxy)-2,3-dichlorobenzyl)-9H-purin-6-amine;

(*R*)-9-(6-((4-amino-5-(methylthio)pentyl)oxy)-2,3-dichlorobenzyl)-9*H*-purin-6-amine; and

(*R*)-5-(2-((6-amino-9*H*-purin-9-yl)methyl)-3,4-dichlorophenoxy)-N^1,N^1-dimethylpentane-1,2-diamine;

or a pharmaceutically acceptable salt thereof.

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

15. A combination comprising a compound according to any one of claims 1-13, and one or more therapeutically active agent.

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

17. Use of a compound according to any of claims 1-13 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).

18. The use of claim 17, 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.

19. The use of claim 17, wherein said disease or condition that benefit from or is treatable by inhibition of MLL1 is breast cancer, cervical cancer, skin cancer (particularly skin squamous cell carcinoma), 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 (particularly acute lymphoblastic leukemia), non-Hodgkin's lymphoma (particularly mantle cell lymphoma) or pulmonary arterial hypertension.

20. The use of claim 19, wherein said disease or condition that benefit from or is treatable by inhibition of MLL1 is acute lymphoblastic leukaemia, skin squamous cell carcinoma or mantle cell lymphoma.