PIPERIDINYL-METHYL-PURINEAMINES AS NSD2 INHIBITORS AND ANTI-CANCER AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of PCT/CN2019/100542 filed 14 August 2019, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods for inhibiting the nuclear SET domain-containing protein 2 (NSD2).

BACKGROUND OF THE INVENTION

The nuclear receptor–binding SET domain protein 2 (NSD2), also known as Wolf-Hirschhorn syndrome candidate 1 (WHSC1) or multiple myeloma SET domain (MMSET) is an epigenetic modifier, and is believed to have a driving role in oncogenesis. Both NSD2 overexpression and point mutations that increase its catalytic activity are associated with several human cancers. (Coussens et al., J. Biol. Chem. 293, 13750-13654 (2018).

NSD2 is dysregulated by the t(4;14)(p16.3;q32.3) translocation in approximately 15% of multiple myeloma (MM) cases. Increased expression of NSD2 in t(4;14)+ MM cell lines is associated with increased levels of H3K36me2 and reciprocally decreased levels of H3K27me3. Such correlation suggests a causal relationship between NSD2 histone methyltransferase (HMT) activity and the MM oncogene.

High expression of the NSD2 protein has been demonstrated in different human cancer types, including bladder, brain, gastrointestinal, lung, liver, ovary, skin, uterus, breast, prostrate and glioblastoma. (Coussens et al., supra; Ezponda et al., Oncogene 32:2882-2890 (2013)). Notably, NSD2 is among the most frequently mutated genes in pediatric cancer genomes. The NSD2 SET domain variant, E1099K, was identified in both acute lymphoblastic leukemia tumors and cell lines with increased H3K36me2 that lack the t(4;14) translocation. Sequence results of >1000 pediatric cancer genomes, representing 21 different cancers, revealed the E1099K variant in 14% of t(12;21) ETV6 -RUNX1 containing acute lymphoblastic leukemia (ALL). NSD2 is also among the most frequently mutated genes found in mantle cell lymphoma tumors, where both E1099K and T1150A variants are observed. The E1099K variant has also been reported in chronic lymphocytic leukemia (CLL), lung and stomach cancers. (Coussens et al., supra). In general, NSD2 upregulation is associated with aggressive tumor behavior and poor prognosis. (Ezponda et al., supra).

NSD2 is a promising target for cancer therapy, and there remains a need for selective inhibitors of NSD2.

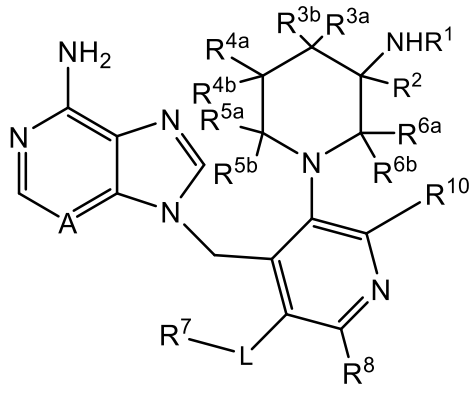
~~SUMMARY OF THE INVENTION~~

~~The present invention provides novel compounds that inhibit NSD2; and compositions and methods for treating or preventing a disease or condition mediated by NSD2.~~

SUMMARY

The present disclosure provides novel compounds that inhibit NSD2; and compositions and methods for treating or preventing a disease or condition mediated by NSD2.

In an aspect of the present disclosure, there is provided a compound of Formula (I)



(I)

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

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

L is a bond or C_{1-4} alkylene;

R^1 is H; or

R^1 and R^2 together with NH forms a 5-8 membered heterocyclyl containing 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) hydrogen, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-6} alkoxyC_{1-6} alkylene or -C_{3-8} cycloalkoxy(C_{1-6} alkyl);

(ii) cyano; -cyanoC_{1-6} alkylene; -C_{1-6} alkylthioC_{1-6}alkyl; -C_{2-6} alkenyl; -haloC_{2-6} alkenyl; -C_{2-6} alkynyl; -C_{1-4} alkylSOC_{1-4}alkyl; -C_{1-4} alkylSO_2C_{1-4}alkyl; -SO_2R^8 or -C(C_{1-4} alkyl)=N-O(C_{1-4} alkyl);

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

(iv) -$(CR^aR^b)_r$-C(=O)-$NR^{12}R^{13}$ wherein R^{12} is hydrogen or C_{1-6} alkyl; R^{13} is hydrogen, -C_{1-6} alkyl or a 5-6 membered heterocyclic ring; or R^{12} and R^{13} together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C_{1-4} alkyl;

(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

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

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

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} alkylene, -C_{1-6} alkoxy, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-6} alkoxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, 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 is H, -C_{1-4} alkoxy, halo or C_{1-4} alkyl; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R^8 is C_{3-8} cycloalkyl(C_{0-6} alkyl); 4-6 membered heterocyclylC_{0-6}alkyl comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroarylC_{0-6}alkyl comprising 1-3 heteroatoms selected from N, O and S; wherein R^8 is unsubstituted or substituted by 1-3 R^{17};

R^{17} is halo, hydroxy, cyano, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -C_{1-6} alkoxy, -haloC_{1-6} alkoxy, -$NR^aC(=O)CR^c=C(R^c)_2$ or -$(CR^aR^b)_t$-NR^a-C(=O)-R^{18};

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

R^{18} is -C_{1-4} alkyl or -C_{1-4} haloalkyl; and

p, q, r, s and t are independently 0-4.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier.

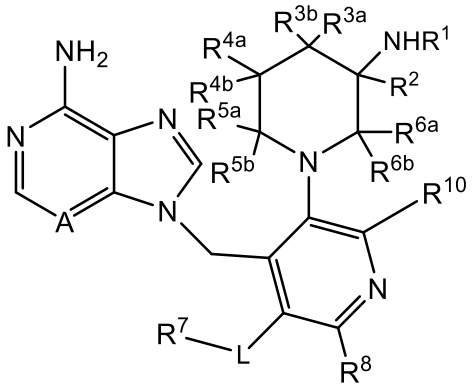
In a further aspect of the present disclosure, there is provided a combination comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agent.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2).

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein and optionally in combination with a second therapeutic agent, in the manufacture of a medicament for a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2).

In another aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutically acceptable salt thereof, for use in therapy.

In one ~~aspect~~example, the ~~invention~~ present disclosure provides a compound of Formula (I):



(I)

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

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

L is a bond or C_{1-4} alkylene;

R^1 is H; or

R^1 and R^2 together with NH forms a 5-8 membered heterocyclyl containing 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) hydrogen, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-6} alkoxyC_{1-6} alkylene or -C_{3-8} cycloalkoxy(C_{1-6} alkyl);

(ii) cyano; -cyanoC_{1-6} alkylene; -C_{1-6} alkylthioC_{1-6}alkyl; -C_{2-6} alkenyl; -haloC_{2-6} alkenyl; -C_{2-6} alkynyl; -C_{1-4} alkylSOC_{1-4}alkyl; -C_{1-4} alkylSO_2C_{1-4}alkyl; -SO_2R^8 or -C(C_{1-4} alkyl)=N-O(C_{1-4} alkyl);

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

(iv) -$(CR^aR^b)_r$-C(=O)-$NR^{12}R^{13}$ wherein R^{12} is hydrogen or C_{1-6} alkyl; R^{13} is hydrogen, -C_{1-6} alkyl or a 5-6 membered heterocyclic ring; or R^{12} and R^{13} together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C_{1-4} alkyl;

(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

(vi) 5-9 membered heteroarylC_{0-6}alkyl or 5-9 membered heteroaryl(haloC_{1-4}alkyl), wherein each said heteroaryl radical is unsubstituted or substituted by -C_{1-4} alkyl, -haloC_{1-4} alkyl, -hydroxyC_{1-4} alkylene, -C_{1-4} alkoxy,- haloC_{1-4} alkoxy, halo, hydroxy, cyano, oxido, -aminocarbonylC_{0-6}alkyl, -C_{1-4}alkylaminocarbonylC_{0-6}alkyl, -diC_{1-4}alkylaminocarbonylC_{0-6}alkyl or -C_{3-7} cycloalkyl;

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} alkylene, -C_{1-6} alkoxy, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-6} alkoxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, 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 is H, -C_{1-4} alkoxy, halo or C_{1-4} alkyl; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R^8 is C_{3-8} cycloalkyl(C_{0-6} alkyl); 4-6 membered heterocyclylC_{0-6}alkyl comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroarylC_{0-6}alkyl comprising 1-3 heteroatoms selected from N, O and S; wherein R^8 is unsubstituted or substituted by 1-3 R^{17};

R^{17} is halo, hydroxy, cyano, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -C_{1-6} alkoxy, -haloC_{1-6} alkoxy, -$NR^aC(=O)CR^c=C(R^c)_2$ or -$(CR^aR^b)_t$-NR^a-C(=O)-R^{18};

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

R^{18} is -C_{1-4} alkyl or -C_{1-4} haloalkyl; and

p, q, r, s and t are independently 0-4.

In another ~~aspect~~example, the ~~invention~~ present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) or sub-formulae thereof, or a pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable carriers.

In yet another ~~aspect~~example, the ~~invention~~ present disclosure provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of a compound of Formula (I) or sub-formulae thereof, or a pharmaceutically acceptable salt thereof; and one or more therapeutically active agent(s).

The compounds of the ~~invention~~ present disclosure, alone or in combination with one or more therapeutically active agent(s), can be used for treating or preventing a disease or condition mediated by NSD2; and more particularly wherein the disease or condition is characterized by overexpression or undesired upregulation of NSD2.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions and methods for treating or preventing a disease or condition mediated by NSD2.

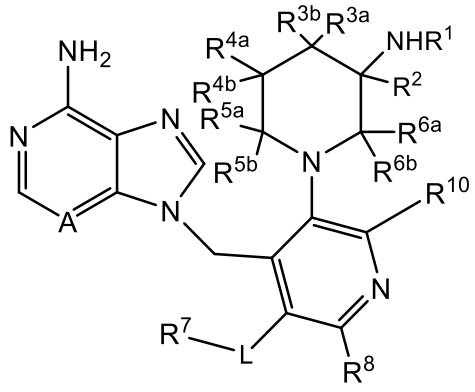
Definitions

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

As used herein, the term "-C_{1-6}alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond. The term "C_{1-4}alkyl" is to be construed accordingly. Examples of C_{1-6}alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl and 1,1-dimethylethyl (*t*-butyl).

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^9 wherein R^9 is hydrogen or halo;

L is a bond or C_{1-4} alkylene;

R^1 is H; or

R^1 and R^2 together with NH forms a 5-8 membered heterocyclyl containing 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) hydrogen, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-6} alkoxyC_{1-6} alkylene or -C_{3-8} cycloalkoxy(C_{1-6} alkyl);

(ii) cyano; -cyanoC_{1-6} alkylene; -C_{1-6} alkylthioC_{1-6}alkyl; -C_{2-6} alkenyl; -haloC_{2-6} alkenyl; -C_{2-6} alkynyl; -C_{1-4} alkylSOC_{1-4}alkyl; -C_{1-4} alkylSO_2C_{1-4}alkyl; -SO_2R^8 or -C(C_{1-4} alkyl)=N-O(C_{1-4} alkyl);

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

(iv) -$(CR^aR^b)_r$-C(=O)-$NR^{12}R^{13}$ wherein R^{12} is hydrogen or C_{1-6} alkyl; R^{13} is hydrogen, -C_{1-6} alkyl or a 5-6 membered heterocyclic ring; or R^{12} and R^{13} together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C_{1-4} alkyl;

(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

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

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

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} alkylene, -C_{1-6} alkoxy, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-6} alkoxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, 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 is H, -C_{1-4} alkoxy, halo or C_{1-4} alkyl; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R^8 is C_{3-8} cycloalkyl(C_{0-6} alkyl); 4-6 membered heterocyclylC_{0-6}alkyl comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroarylC_{0-6}alkyl comprising 1-3 heteroatoms selected from N, O and S; wherein R^8 is unsubstituted or substituted by 1-3 R^{17};

R^{17} is halo, hydroxy, cyano, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -C_{1-6} alkoxy, -haloC_{1-6} alkoxy, -$NR^aC(=O)CR^c=C(R^c)_2$ or -$(CR^aR^b)_t$-NR^a-C(=O)-R^{18};

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

R^{18} is -C_{1-4} alkyl or -C_{1-4} haloalkyl; and

p, q, r, s and t are independently 0-4.

2. The compound of Formula (I) in claim 1 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein A is N.

3. The compound of Formula (I) in claim 1 or 2, or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt; wherein

R^{3a} is hydrogen or halo; and R^{3b} is hydrogen, halo, -hydroxyl, -C_{1-6} alkoxy or cyano; or

R^{4a} is hydrogen or halo; and R^{4b} is hydrogen, halo, -C_{1-6}alkoxyC_{1-6}alkylene, -C_{1-6} alkyl or -haloC_{1-6} alkyl; or

R^{5a} is hydrogen and R^{5b} is hydrogen or -C_{1-6} alkyl; or

R^{5a} and R^{5b} together form an oxo substituent.

4. The compound of Formula (I) in any one of claims 1-3 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt; wherein:

R^{6a} is hydrogen or halo;

R^{6b} is hydrogen, -haloC_{1-6} alkoxyC_{1-6} alkylene, -hydroxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, carboxyl, phenyl or -$(CR^aR^b)_t$-C(O)-$NR^{15}R^{16}$;

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

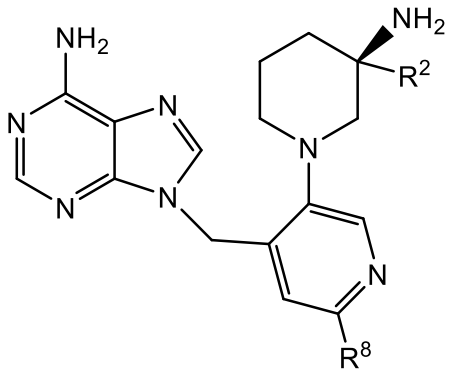
t is 0-1; or

R^{6a} and R^{6b} together form an oxo substituent.

5. The compound of Formula (I) in any one of claims 1-4 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^7 is H, -C_{1-4} alkoxy or halo.

6. The compound of Formula (I) in any one of claims 1-5 or a pharmaceutically acceptable salt thereof; wherein R^1, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a}, R^{6b} and R^7 are hydrogen.

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

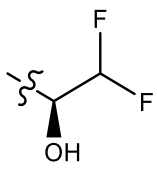
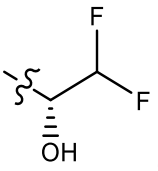


(II)

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

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^2 is hydrogen, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -hydroxyC_{1-6} alkylene, -hydroxyhaloC_{1-6} alkylene, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-6} alkoxyC_{1-6} alkylene or -C_{3-8} cycloalkoxy(C_{1-6} alkyl).

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^2 is hydrogen; 2,2-difluoroethyl; 2-methyl-propan-1-olyl; ethan-1-olyl; 2,2-difluoroethan-1-olyl; 2-fluoroethan-1-olyl; 2,2,2-trifluoroethan-1-olyl; difluoromethoxyl; or 2,2,2-trifluoroethoxyl.

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^2 is  or .

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^2 is -C_{1-4}alkylcarbonyl;

-$(CR^aR^b)_p$-C(O)-OR^{10} wherein R^{10} is hydrogen or -C_{1-4} alkyl;

-C(O)-$(CR^aR^b)_q$-R^{11} wherein R^{11} is C_{3-6} 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; or

-$(CR^aR^b)_r$-C(O)-$NR^{12}R^{13}$; wherein

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

R^{13} is hydrogen, -C_{1-6} alkyl or a 5-6 membered heterocyclic ring; or

R^{12} and R^{13} together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with -C_{1-4} alkyl; and

R^a, R^b and R^{11} are independently hydrogen or -C_{1-4} alkyl; and

p, q and r are independently 0-2.

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^2 is selected from the group:

pyridin-2-yl, (pyridin-2-yl)methyl or (pyridin-2-yl)ethyl, wherein said pyridin-2-yl is independently unsubstituted or substituted with 1-2 -C_{1-4} alkyl, -C_{1-4} haloalkyl, hydroxyl, -hydroxyC_{1-4} alkylene, cyano, -C_{1-4} alkoxy, -C_{1-6}alkoxyC_{1-6}alkylene, -haloC_{1-4} alkoxy, halo or -C_{3-7} cycloalkyl;

thiazol-4-yl, thiazol-2-ylmethyl, oxazol-2-yl, oxazol-2-ylmethyl, pyridazin-3-yl, pyridazin-3-ylmethyl, pyrazin-2-yl, pyrazin-2-ylmethyl, pyrimidin-4-yl, pyrimidin-4-ylmethyl, each of which is independently unsubstituted or substituted with -C_{1-4} alkyl or halo;

1H-pyrazol-3-yl, (1H-pyrazol-3-yl)methyl, 1-methyl-1H-pyrazol-4-yl, (1,2,3-triazol-4-yl), isoxazol-3-yl, each of which is independently unsubstituted or substituted with -C_{1-4} alkyl, halo or -C_{3-7} cycloalkyl;

1,4-dioxan-2-yl;

pyridin-2(1H)-onyl; and

pyridin-1-oxide-2-yl.

13. The compound according to any one of claims 1-12 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^8 is cyclopropyl; cyclobutyl; cyclohexyl or azetidinyl.

14. The compound according to any one of claims 1-12 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^8 is 2,3-dihydrobenzofuran-5-yl; 1,3-dihydroisobenzofuran-5-yl; benzo[d][1,3]dioxol-5-yl; imidazo[1,2-a]pyridin-6-yl or pyrazolo[1,5-a]pyridine-6-yl.

15. The compound according to any one of claims 1-12 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^8 is pyridyl, unsubstituted or substituted with 1-2 halo, -C_{1-6} alkyl or -C_{1-6} alkoxy; 1H-indazol-5-yl unsubstituted or substituted with 1-2 halo or -C_{1-6} alkyl; or 1H-benzo[d]-imidazol-6-yl unsubstituted or substituted with -C_{1-6} alkyl.

16. The compound according to any one of claims 1-12 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^8 is phenyl substituted with 1-3 R^{17};

R^{17} is halo, hydroxy, cyano, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -C_{1-6} alkoxy, -haloC_{1-6} alkoxy, -$NR^dC(O)CR^d$=$C(R^d)_2$ or -$(CR^aR^b)_t$-NR^d-C(O)-R^{18};

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

R^{18} is C_{1-4} haloalkyl; and

t is 0-1.

17. The compound according to any one of claims 1-12 or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof; wherein R^8 is phenyl substituted with 1-3 R^{17}; and R^{17} is halo, hydroxy, -C_{1-6} alkyl, -haloC_{1-6} alkyl, -C_{1-6} alkoxy or -haloC_{1-6} alkoxy.

18. 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.

19. A pharmaceutical composition comprising a compound according to any one of claims 1-18 or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier.

20. A combination comprising a compound according to any one of claims 1-18 or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agent.

21. The combination according to claim 20, wherein said one or more therapeutically active agent is an anti-cancer agent, an analgesic or an anti-inflammatory agent.

22. ~~A method for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2), comprising administering to a subject in need of such treatment a therapeutically effective amount of a~~ Use of a compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2).

23. The ~~method~~ use of claim 22, wherein said disease or condition mediated by NSD2 is selected from solid tumors, leukemia, myeloma, lymphoma and hypertension.

24. The ~~method~~ use of claim 23, wherein said disease or condition mediated by NSD2 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.

25. The ~~method~~ use of claim 22, wherein said disease or condition mediated by NSD2 is acute lymphoblastic leukaemia, skin squamous cell carcinoma or mantle cell lymphoma.

26. 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 mediated by nuclear SET domain-containing protein 2 (NSD2).

27. A compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, for use in therapy.