Elevated levels of LSD1 have been found in diverse cancers and shows close relationship with many cellular effects such as epithelial-mesenchymal transition (EMT), cell proliferation and differentiation, stem cell biology, and malignant transformation (Abdel-Magid AF. Lysine-specific demethylase 1 (LSD-1) inhibitors as potential treatment for different types of cancers. ACS Medicinal Chemistry Letters. 2017; 8:1134–5). LSD1 inactivation also enhances anti-tumor immunity and inhibits checkpoint blockade (Sheng W., et al. LSD1 ablation stimulates anti-tumor immunity and enables checkpoint blockade. Cell. 2018; 174:549–63). LSD1 dysfunction is also associated with the development of ALL (acute lymphoblastic leukemia) and AML (acute myeloid leukemia) (Mould D. P., et. al. Reversible inhibitors of LSD1 as therapeutic agents in acute myeloid leukemia: clinical significance and progress to date. Medicinal Research Reviews. 2015; 35:586–618)

Further, high expression levels of LSD1 have also been found in breast cancer, neuroblastoma, colorectal cancer, and prostate cancer. Aberrant dysregulation of LSD1 causes differentiation arrest in both hematological and solid tumors, making it a potential target for cancer therapy (P. Troyer, Medical Epigenetics (Second Edition, 2021, LSD-1 functions in activation and repression of transcription).

Numerous LSD1 inhibitors have been reported to date, some of them such as TCP, ORY-1001, GSK-2879552, IMG-7289, INCB059872, CC-90011, and ORY-2001 (Vafidemstat) have been approved or currently undergo clinical assessment for cancer therapy, particularly for small lung cancer cells (SCLC) and acute myeloid leukaemia (AML). However, blood brain barrier (BBB) penetration of these medications remains poor. Therefore, the above mentioned therapies remain unavailable for the treatment of cancers affecting the brain or the central nervous system such as brain tumours (e.g. glioblastoma) and CNS leukaemia.

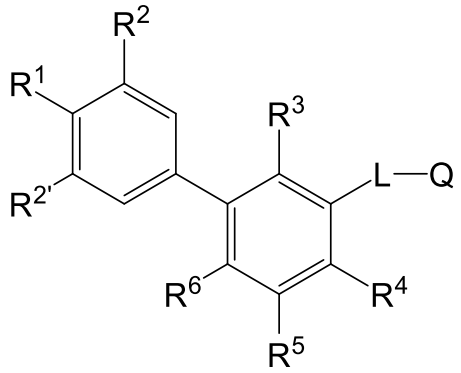
To date there is no effective and approved medical treatment available with good BBB penetration properties which is based on the inhibition of LSD1.

The present invention has been devised with the above observations in mind.

SUMMARY

Generally, provided herein are compounds and pharmaceutical compositions capable of inhibiting LSD1. Also provided are method of treatment and therapeutic / medical uses involving compounds or pharmaceutical compositions of this disclosure for inhibiting LSD1 and, particularly, for treating diseases, disorders or conditions associated with LSD1.

In this disclosure, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, prodrug, pharmaceutically active metabolite thereof or combinations thereof:



(I),

wherein

R^1 is nitro or cyano;

R^2 and $R^{2'}$ are each independently selected from C_{1-3} alkyl, hydrogen or halogen;

R^3 is selected from hydrogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 heterocycloalkyl, C_4-C_5 heterocycloalkenyl, C_3-C_5 heterocycloalkyl C_1-C_3 alkyl, C_5-C_6 aryl, C_3-C_6 heteroaryl, $C_{1-}C_4$ alkoxyl, $C_{3-}C_6$ cycloalkyl-C_1-C_3 alkoxyl, $C_{1-}C_4$ haloalkoxyl, $C_{1-}C_3$ haloalkyl, halogen, amino, alkylamino, dialkylamino, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic heterocyclic amine, cyano, wherein each alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkyl alkyl, aryl, heteroaryl, alkoxyl, cycloalkyl alkoxyl, alkylamino, dialkylamino, cyclic amine, heterocyclic amine, unsaturated or aromatic cyclic amine, and unsaturated or aromatic heterocyclic amine is optionally substituted with 1 to 3 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, C_3-C_6 cycloalkyl, hydroxyl, halogen, amino;

R^4 is selected from hydrogen or halogen;

R^5 is selected from the group consisting of hydrogen, C_{1-3} alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 aryl, C_3-C_6 heteroaryl, halogen, amino, alkylamino, dialkylamino, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic heterocyclic amine, wherein each alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, alkylamino, dialkylamino, cyclic amine, heterocyclic amine, unsaturated or aromatic cyclic amine, and unsaturated or aromatic heterocyclic amine is optionally substituted with 1 to 3 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, C_3-C_6 cycloalkyl, hydroxyl, halogen, or amino;

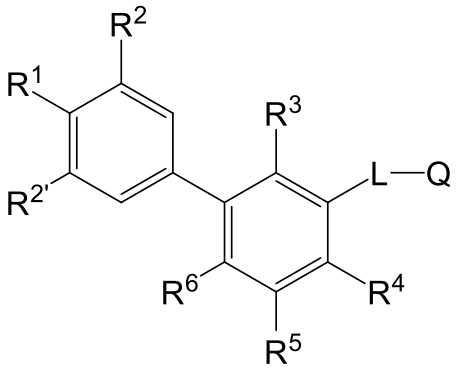
R^6 is selected from the group consisting of hydrogen, $C_{1-}C_4$ alkyl, $C_{1-}C_4$ alkoxyl, amino, alkylamino, aminoalkyl, dialkylamino, $C_{8—}C_{11}$ spirocycloalkyl, C_5-C_{10} heterospirocycloalkyl, C_5-C_{11} monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic

heterocyclic amine, $C_{7-}C_{10}$ spirocyclic amine, $C_{4-}C_9$ heterospirocyclic amine, C_3-C_6 heteroaryloxyl, or C_3-C_6 cycloalkoxyl, wherein each is optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, amino, C_1-C_6 alkyl, C_1-C_6 alkoxyl, halogen, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_5 heterocycloalkyl, or optionally substituted C_3-C_6 heteroaryl, wherein said optionally substituted cycloalkyl, heterocycloalkyl and heteroaryl may be substituted with 1 or 2 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, hydroxyl, halogen or amine;

L is a linker selected from the group consisting of a bond, -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -C≡C-, -CH_2-O-, -C(O)-, -O-, -O-CH_2-, -NH-CH_2-, -$N(CH_3)$-CH_2-, --NH-C(O)-, -$N(CH_3)$-C(O)-, -CH_2-NH-CH_2-

Q is a monocyclic or bicyclic ring system selected from the group consisting of C_5-C_9 cycloalkyl, C_4-C_8 heterocycloalkyl, $C_{8-}C_{11}$ spirocycloalkyl, C_5-C_{10} heterospirocycloalkyl, C_3-C_8 cyclic amine, C_3-C_8 heterocyclic amine, $C_{7-}C_{10}$ spirocyclic amine, or $C_{4-}C_9$ heterospirocyclic amine, wherein each cycloalkyl or heterocycloalkyl group may be saturated or unsaturated, said bicyclic ring may be a fused or bridged bicycle, and wherein Q is optionally substituted with 1 to 3 R^7, wherein each R^7 is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylcarbonyl, hydroxyl, oxo, halogen, C_1-C_6 alkylamine or amino.

In an aspect of the present disclosure, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I),

wherein

R^1 is nitro or cyano;

R^2 and $R^{2'}$ are each independently selected from C_{1-3} alkyl, hydrogen or halogen

R^3 is selected from hydrogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 heterocycloalkyl, C_4-C_5 heterocycloalkenyl, C_3-C_5 heterocycloalkyl C_1-C_3 alkyl, C_5-C_6 aryl, C_3-C_6 heteroaryl, C_1-C_4 alkoxyl, C_3-C_6 cycloalkyl-C_1-C_3 alkoxyl, C_1-C_4 haloalkoxyl, C_1-C_3 haloalkyl, halogen, amino, alkylamino, dialkylamino, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic heterocyclic

amine, cyano, wherein each alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkyl alkyl, aryl, heteroaryl, alkoxyl, cycloalkyl alkoxyl, alkylamino, dialkylamino, cyclic amine, heterocyclic amine, unsaturated or aromatic cyclic amine, and unsaturated or aromatic heterocyclic amine is optionally substituted with 1 to 3 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, C_3-C_6 cycloalkyl, hydroxyl, halogen, amino;

R^4 is selected from hydrogen or halogen;

R^5 is selected from the group consisting of hydrogen, C_{1-3} alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 aryl, C_3-C_6 heteroaryl, halogen, amino, alkylamino, dialkylamino, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic heterocyclic amine, wherein each alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, alkylamino, dialkylamino, cyclic amine, heterocyclic amine, unsaturated or aromatic cyclic amine, and unsaturated or aromatic heterocyclic amine is optionally substituted with 1 to 3 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, C_3-C_6 cycloalkyl, hydroxyl, halogen, or amino;

R^6 is selected from the group consisting of hydrogen, $C_{1-}C_4$ alkyl, $C_{1-}C_4$ alkoxyl, amino, alkylamino, aminoalkyl, dialkylamino, C_8—C_{11} spirocycloalkyl, C_5-C_{10} heterospirocycloalkyl, C_5-C_{11} monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic heterocyclic amine, C_7—C_{10} spirocyclic amine, C_4—C_9 heterospirocyclic amine, C_3-C_6 heteroaryloxyl, or C_3-C_6 cycloalkoxyl wherein each is optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, amino, C_1-C_6 alkyl, C_1-C_6 alkoxyl, halogen, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_5 heterocycloalkyl, or optionally substituted C_3-C_6 heteroaryl, wherein said optionally substituted cycloalkyl, heterocycloalkyl and heteroaryl may be substituted with 1 or 2 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, hydroxyl, halogen or amine;

L is a linker selected from the group consisting of a bond, -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -C≡C-, -CH_2-O-, -C(O)-, -O-, -O-CH_2-, -NH-CH_2-, -N(CH_3)-CH_2-, --NH-C(O)-, -N(CH_3)-C(O)-, -CH_2-NH-CH_2-;

Q is a monocyclic or bicyclic ring system selected from the group consisting of C_5-C_9 cycloalkyl, C_4-C_8 heterocycloalkyl, $C_{8-}C_{11}$ spirocycloalkyl, C_5-C_{10} heterospirocycloalkyl, C_3-C_8 cyclic amine, C_3-C_8 heterocyclic amine, C_7—C_{10} spirocyclic amine, or C_4—C_9 heterospirocyclic amine, wherein each cycloalkyl or heterocycloalkyl group may be saturated or unsaturated, said bicyclic ring may be a fused or bridged bicycle, and wherein Q is optionally substituted with 1 to 3 R^7, wherein each R^7 is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylcarbonyl, hydroxyl, oxo, halogen, C_1-C_6 alkylamine or amino.

In examples, each heteroaryl or heterocyclic substituent may include from 1 to 4, 1 to 3, or 1 or 2 heteroatoms independently selected from O, S and N.

In examples each heteroaryl or heterocyclic substituent may be connected to the remainder of the compound through a carbon atom, or through a heteroatom. In examples, the heteroaryl or heterocyclic substituent is connected to the remainder of the compound through a carbon atom, or through a N atom.

Suitably, one of R^2 and $R^{2'}$ may be hydrogen and the other may be F; one of R^2 and $R^{2'}$ may be hydrogen and the other may be Cl; or both R^2 and $R^{2'}$ may be hydrogen. In some particular examples one of R^2 and $R^{2'}$ may be methyl and the other may be hydrogen, F or Cl.

Suitably, R^3 may be selected from hydrogen, halogen, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, C_5-C_6 aryl, C_3-C_6 heteroaryl, or C_2-C_5 heterocyclic amine. In various examples, R^3 may be hydrogen or Cl; R^3 may be an optionally substituted 5 or 6 membered heteroaryl; R^3 may be an optionally substituted 4 to 6 membered heterocycloalkyl; or R^3 may be an optionally substituted 3 to 5 membered cycloalkyl; wherein each hetero moiety may include 1 or 2 heteroatoms independently selected from O, S and N; and/or wherein any optional substituents are independently selected from 1 or 2 substituents of the group consisting of methyl, F and Cl. In examples, R3 is optionally substituted oxazole.

In various examples R^4 may be hydrogen; R^4 may be F and R^5 and R^6 may each be hydrogen; R^4 may be F and R^5 and R^6 may each be hydrogen; or R^4, R^5 and R^6 may all be hydrogen.

In examples R^5 may be hydrogen; R^5 may be F; R^5 may be a 4 or 5 membered heterocycloalkyl; R^5 may be C_1-C_3 alkyl; R^5 may be 3, 4 or 5 membered cycloalkyl; or R^5 may be optionally substituted C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 heterocycloalkyl, C_3-C_6 aryl or C_3-C_6 heteroaryl. Particularly, R^5 can be selected from hydrogen, F, methyl or pyrrolidine.

In various examples R^4, R^5 and R^6 are hydrogen.

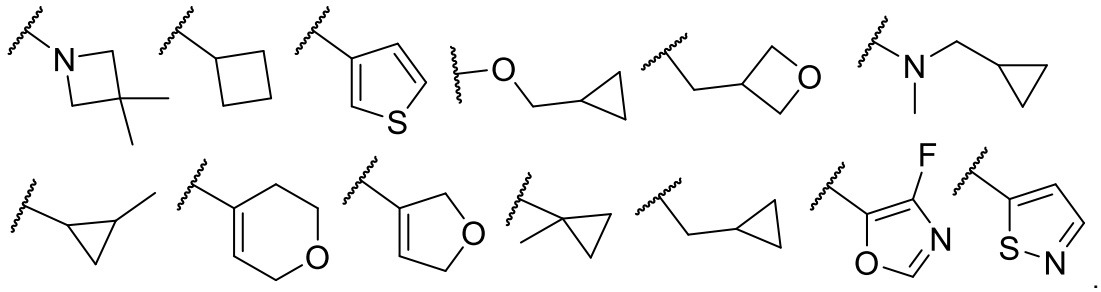
In examples R^6 may be hydrogen; R^6 may be F or Cl; R^6 may be an optionally substituted 4 or 5 membered heterocycloalkyl; R^6 may be an optionally substituted 8, 9 or 10 membered bicyclic or spirocyclic heterocycloalkyl; R^6 may be an optionally substituted 5 or 6 membered heteroaryl; R^6 may be an optionally substituted 4, 5 or 6 membered cycloalkyl or spirocycloalkyl; R^6 may be a C_1-C_3 haloalkoxy; or R^6 may be a C_2-C_8 alkylamine or dialkylamine, wherein each hetero moiety may include 1 or 2 heteroatoms independently selected from O, S and N; and/or wherein any optional substituents are independently selected from 1 or 2 substituents from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxyl, F, Cl and hydroxyl. Particularly, R^6 can be selected from hydrogen, F, methyl or pyrollidine.

In various examples L may suitably be selected from -CH_2- or -CH_2-CH_2-.

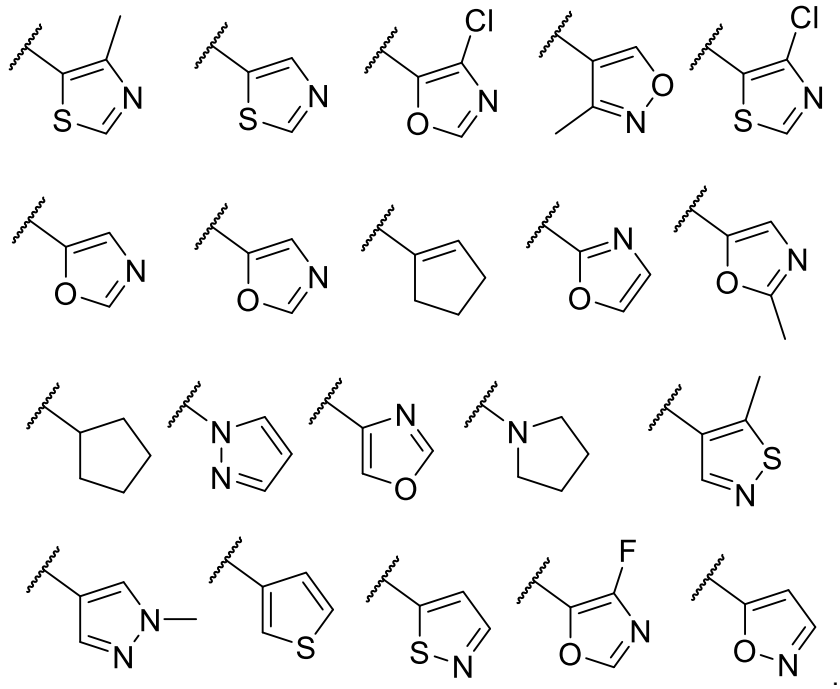
Suitably, Q may be selected from the group consisting of optionally substituted 5 to 7 membered heterocycloalkyl and optionally substituted 4 to 7 membered mono or fused or bridged bicycloalkylamine; wherein each hetero moiety may include 1 or 2 heteroatoms independently selected from O and N; and/or wherein any optional substituents are independently selected from 1 to 3 substituents from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxyl, C_1-C_3 alkylamine, C_1-C_3 dialkylamine, C_1-C_3 carbonyl, amine, amino-C_1-C_3 alkyl, oxo, F, Cl and hydroxyl.

In examples, R^7 may be independently selected from C_1-C_3 alkyl, C_1-C_3 haloalkyl, hydroxyl, oxo, F, C_1-C_3 alkylamino, C_1-C_3 dialkylamino or amino; or R^7 may be independently selected from methyl, ethyl, amine and F; optionally wherein there are 1, 2 or 3 R^7 groups.

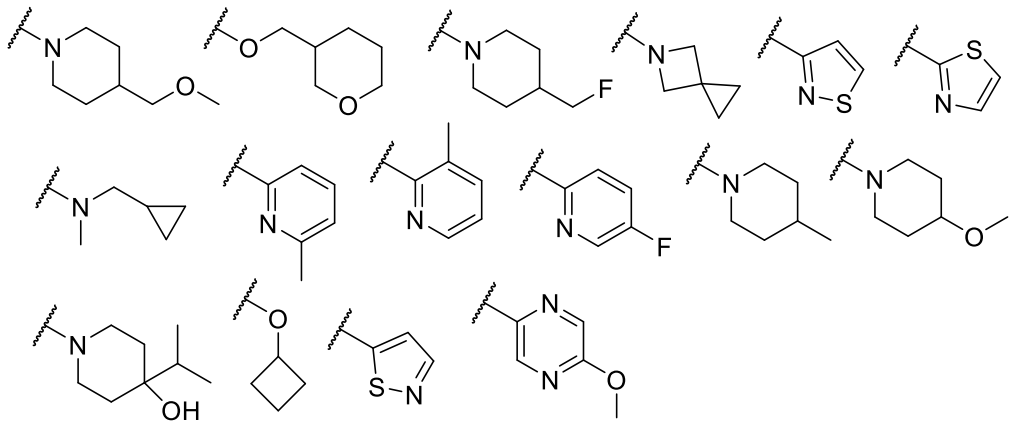
In some beneficial examples, R^3 may be selected from the group consisting of the following structures:



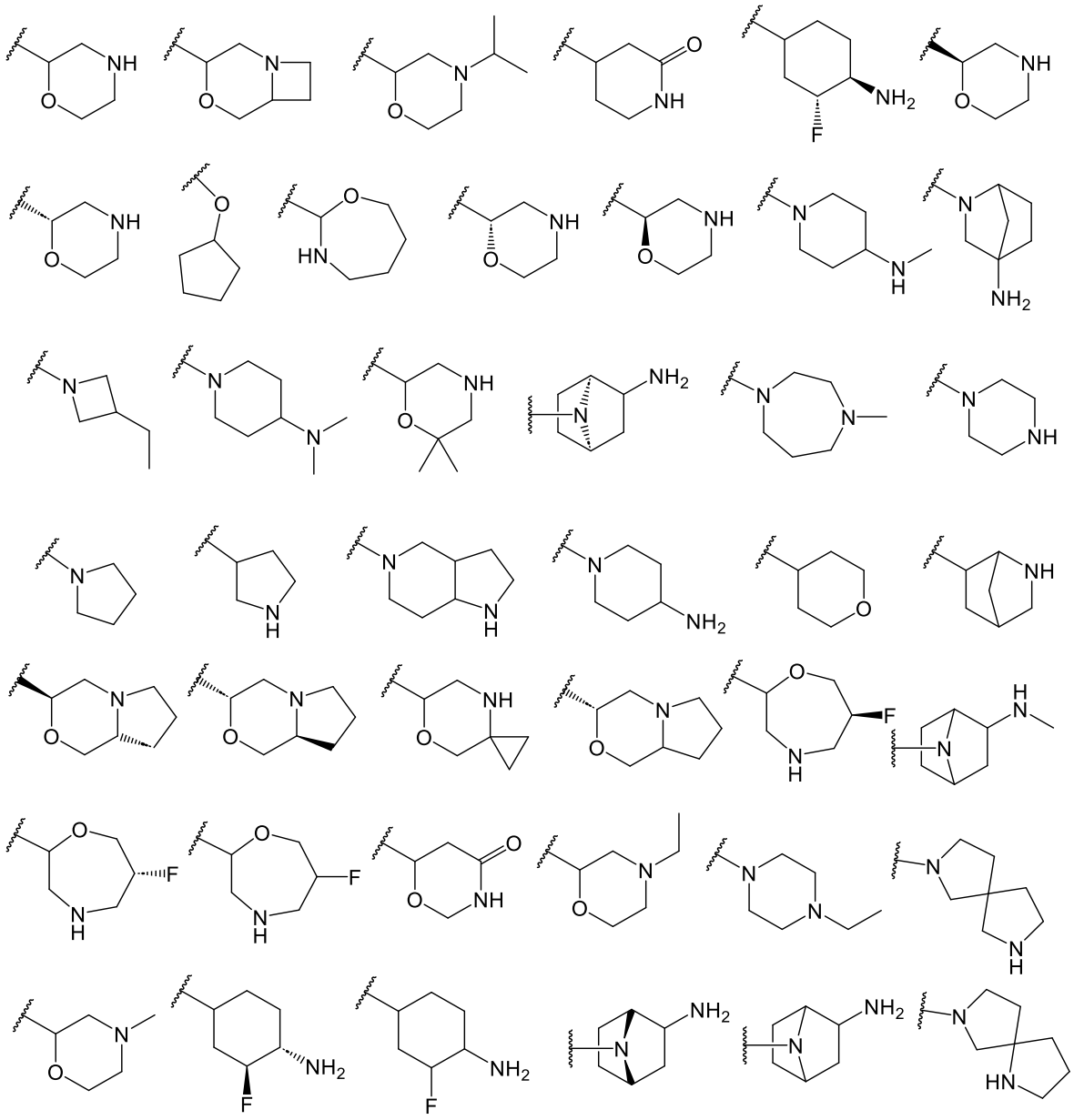
In some beneficial examples, R^5 may be selected from the group consisting of hydrogen and the following structures:



In some beneficial examples, R^6 may be selected from the group consisting of hydrogen and the following structures:

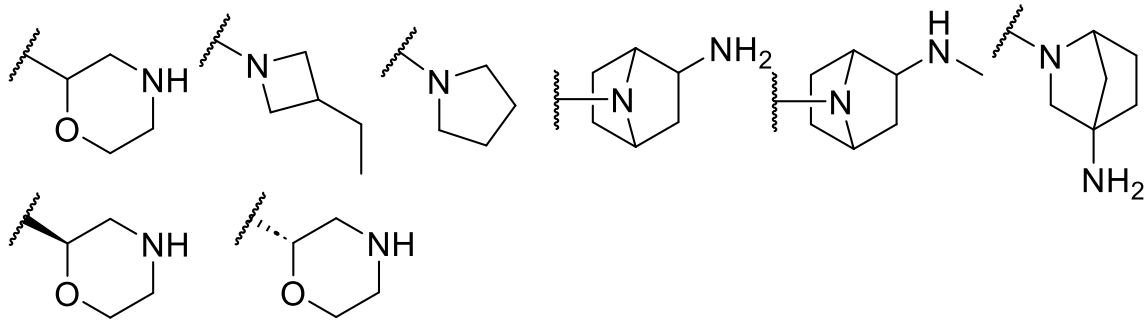


In some beneficial examples, Q may be selected from the group consisting of the following structures:



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Particularly beneficially, Q may be selected from the group consisting of the following structures:



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In examples, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, prodrug, pharmaceutically active metabolite thereof, or combinations thereof, wherein:

R1 is cyano; and/or

R2 and R2' are each independently selected from hydrogen or F; and/or

R3 is selected from hydrogen, propyl, i-propyl, CHF2, cyclopropyl, -CH2-cyclopropyl, -CH2-oxetane, isothiazole, oxazole, fluorooxazole, pyridyl, methoxyl, -O-CH2-cyclopropyl, -O-CH2-CF3, -O-CF3, CF3, Cl, amino, - N(CH3)(CH2-isopropyl), pyrrolidine, cyano; and/or

R4 is hydrogen or F; and/or

R5 is selected from hydrogen, methyl, cyclopropyl, cyclopentenyl, F, amino, NH-CH2-CH2-N(CH3)2; and/or

R6 is selected from hydrogen, -O-cyclobutyl, -O-CH2-oxane, -O-CH2-CH2-CHF2, -O-CH2-CH2-CF3, -O-CH2-CF3, -CH2-O-CHF2, amino, -N(CH3)(CH-(CH3)2, benzimdazole, pyridine; and/or

L is a linker selected from a bond, -CH2-, C≡C-, CH2-NH-CH2-, and/or

Q is C4-C8 heterocycloalkyl which may comprise a further heteroatom selected from N or O; or Q is morpholinyl; and wherein

each heteroaryl, heterocycloalkyl and/or cycloalkyl group is optionally substituted.

In examples, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, prodrug, pharmaceutically active metabolite thereof, or combinations thereof, wherein:

R1 is cyano; and/or

R2 and R2' are each independently selected from hydrogen or F; and/or

R3 is selected from hydrogen, isothiazole, oxazole, fluorooxazole, pyridyl ; and/or

R4 is hydrogen or F; and/or

R5 is selected from hydrogen, methyl, F; and/or

R6 is selected from hydrogen, -O-cyclobutyl, -O-CH2-oxane; and/or

L is a linker selected from a bond, -CH2-, C≡C-; and/or

Q is C4-C8 heterocycloalkyl which may comprise a further heteroatom selected from N or O; or Q is morpholinyl; and wherein
each heteroaryl, heterocycloalkyl and/or cycloalkyl group is optionally substituted.

In particular examples, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, prodrug, pharmaceutically active metabolite thereof, or combinations thereof, wherein:

R1 is cyano;

R2 and R2' are each independently selected from hydrogen or F;

R3 is selected from hydrogen, propyl, i-propyl, CHF2, cyclopropyl, -CH2-cyclopropyl, -CH2-oxetane, isothiazole, oxazole, fluorooxazole, pyridyl, methoxyl, -O-CH2-cyclopropyl, -O-CH2-CF3, -O-CF3, CF3, Cl, amino, - N(CH3)(CH2-isopropyl), pyrrolidine, cyano;

R4 is hydrogen or F;

R5 is selected from hydrogen, methyl, cyclopropyl, cyclopentenyl, F, amino, NH-CH2-CH2-N(CH3)2;

R6 is selected from hydrogen, -O-cyclobutyl, -O-CH2-oxane, -O-CH2-CH2-CHF2, -O-CH2-CH2-CF3, -O-CH2-CF3, -CH2-O-CHF2, amino, -N(CH3)(CH-(CH3)2, benzimdazole, pyridine;

L is a linker selected from a bond, -CH2-, C≡C-, CH2-NH-CH2-,

Q is C4-C8 heterocycloalkyl which may comprise a further heteroatom selected from N or O; or Q is morpholinyl; and

wherein each heteroaryl, heterocycloalkyl and/or cycloalkyl group is optionally substituted.

In some particular examples, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, prodrug, pharmaceutically active metabolite thereof, or combinations thereof, wherein:

R1 is cyano;

R2 and R2' are each independently selected from hydrogen or F;

R3 is selected from hydrogen, isothiazole, oxazole, fluorooxazole, pyridyl ; and/or

R4 is hydrogen or F;

R5 is selected from hydrogen, methyl, F;

R6 is selected from hydrogen, -O-cyclobutyl, -O-CH2-oxane; and/or

L is a linker selected from a bond, -CH2-, C≡C-;

Q is C4-C8 heterocycloalkyl which may comprise a further heteroatom selected from N or O; or Q is morpholinyl; and wherein

each heteroaryl, heterocycloalkyl and/or cycloalkyl group is optionally substituted.

The disclosure, in another aspect, also provides a compound selected from any one of: the group of compounds shown in Table 1; the group of compounds of Table 1 having an IC50 against LSD1 ≤ 1,000 nM;

the group of compounds of Table 1 having an IC50 against LSD1 ≤ 250 nM; the group of compounds of Table 1 having an IC50 against LSD1 ≤ 100 nM; the group of compounds of Table 1 having an IC50 against LSD1 ≤ 50 nM; the group of compounds of Table 1 having an IC50 against LSD1 ≤ 25 nM; or the group of compounds of Table 1 having an IC50 against LSD1 ≤ 10 nM; or a pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof.

The disclosure, in another aspect, provides a compound selected from any one of Examples 1 to 351.

According to the disclosure, there is provided a pharmaceutical composition comprising one or more compound according to the disclosure, or a pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, and one or more pharmaceutically acceptable carrier. In a further aspect of the disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier.

In another aspect, the disclosure provides a compound according to the disclosure or the pharmaceutical composition according to the disclosure for use in medicine. In particular, the compound or pharmaceutical composition may be for use is in the treatment of diseases, conditions or disorders associated with LSD1, such as cancers, oncologic diseases, autoimmune disorders and/or inflammatory diseases.

In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of diseases, conditions or disorders associated with LSD1. In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of cancers, oncologic diseases, autoimmune disorders and/or inflammatory diseases.

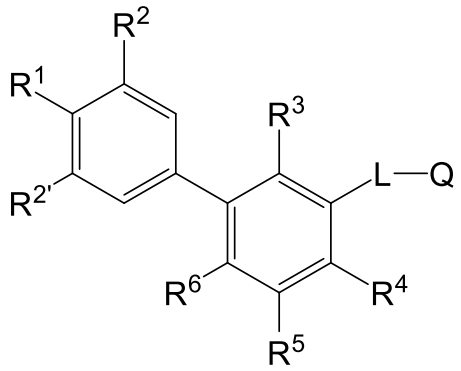
The disclosure provides a method of treating a disease, disorder or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutical composition according to the disclosure.In examples of the uses and methods of this disclosure, the disease, condition or disorder may be selected from the group consisting of: breast, prostate, head and neck, brain, laryngeal, oral and thyroid cancers (e.g. papillary thyroid carcinoma), hematological cancers (e.g. non-Hodgkin lymphoma, B cell lymphoma; chronic myelogenous leukemia), sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers and skin cancers. In examples, the diseases, conditions or disorders selected from the group consisting of: glioblastoma, acute myeloid leukemia (AML) and small cell lung cancer (SCLC). In examples, the disease, condition or disorder is

gliobastoma. In examples, the disease, condition or disorder is acute myeloid leukemia (AML). In examples, the disease, condition or disorder is small cell lung cancer (SCLC).

According to various examples, a compound or pharmaceutical composition may be administered orally, topically, by inhalation, by intranasal administration, or systemically by intravenous, intraperitoneal, subcutaneous, or intramuscular injection. In some examples, the compound or pharmaceutical composition of the disclosure may be administered in combination

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I),

wherein

R^1 is nitro or cyano;

R^2 and $R^{2'}$ are each independently selected from C_{1-3} alkyl, hydrogen or halogen

R^3 is selected from hydrogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 heterocycloalkyl, C_4-C_5 heterocycloalkenyl, C_3-C_5 heterocycloalkyl C_1-C_3 alkyl, C_5-C_6 aryl, C_3-C_6 heteroaryl, C_1-C_4 alkoxyl, C_3-C_6 cycloalkyl-C_1-C_3 alkoxyl, C_1-C_4 haloalkoxyl, C_1-C_3 haloalkyl, halogen, amino, alkylamino, dialkylamino, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic heterocyclic amine, cyano, wherein each alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkyl alkyl, aryl, heteroaryl, alkoxyl, cycloalkyl alkoxyl, alkylamino, dialkylamino, cyclic amine, heterocyclic amine, unsaturated or aromatic cyclic amine, and unsaturated or aromatic heterocyclic amine is optionally substituted with 1 to 3 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, C_3-C_6 cycloalkyl, hydroxyl, halogen, amino;

R^4 is selected from hydrogen or halogen;

R^5 is selected from the group consisting of hydrogen, C_{1-3} alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 aryl, C_3-C_6 heteroaryl, halogen, amino, alkylamino, dialkylamino, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic heterocyclic amine, wherein each alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, alkylamino, dialkylamino, cyclic amine, heterocyclic amine, unsaturated or aromatic cyclic amine, and unsaturated or aromatic heterocyclic amine is optionally substituted with 1 to 3 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, C_3-C_6 cycloalkyl, hydroxyl, halogen, or amino;

R^6 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyl, amino, alkylamino, aminoalkyl, dialkylamino, C_8—C_{11} spirocycloalkyl, C_5-C_{10} heterospirocycloalkyl, C_5-C_{11} monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, C_2-C_7 cyclic amine, C_2-C_5 heterocyclic amine, C_3-C_6 unsaturated or aromatic cyclic amine, C_3-C_5 unsaturated or aromatic

heterocyclic amine, $C_{7-}C_{10}$ spirocyclic amine, $C_{4-}C_9$ heterospirocyclic amine, C_3-C_6 heteroaryloxyl, or C_3-C_6 cycloalkoxyl wherein each is optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxyl, amino, C_1-C_6 alkyl, C_1-C_6 alkoxyl, halogen, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_2-C_5 heterocycloalkyl, or optionally substituted C_3-C_6 heteroaryl, wherein said optionally substituted cycloalkyl, heterocycloalkyl and heteroaryl may be substituted with 1 or 2 substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxyl, hydroxyl, halogen or amine;

L is a linker selected from the group consisting of a bond, -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -C≡C-, -CH_2-O-, -C(O)-, -O-, -O-CH_2-, -NH-CH_2-, -$N(CH_3)$-CH_2-, --NH-C(O)-, -$N(CH_3)$-C(O)-, -CH_2-NH-CH_2-;

Q is a monocyclic or bicyclic ring system selected from the group consisting of C_5-C_9 cycloalkyl, C_4-C_8 heterocycloalkyl, C_8-C_{11} spirocycloalkyl, C_5-C_{10} heterospirocycloalkyl, C_3-C_8 cyclic amine, C_3-C_8 heterocyclic amine, $C_{7-}C_{10}$ spirocyclic amine, or $C_{4-}C_9$ heterospirocyclic amine, wherein each cycloalkyl or heterocycloalkyl group may be saturated or unsaturated, said bicyclic ring may be a fused or bridged bicycle, and wherein Q is optionally substituted with 1 to 3 R^7, wherein each R^7 is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylcarbonyl, hydroxyl, oxo, halogen, C_1-C_6 alkylamine or amino.

2. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1, wherein each heterocyclic or heteroaryl substituent is connected to the remainder of the compound through a carbon atom.

3. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1, wherein the heterocyclic or heteroaryl substituent is connected to the remainder of the compound through a heteroatom.

4. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1, wherein the heterocyclic or heteroaryl substituent comprises at least one N atom, and said heterocyclic or heteroaryl substituent is connected to the remainder of the compound through an N atom.

5. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 4, wherein:

(i) one of R^2 and $R^{2'}$ is hydrogen and the other is F;

(ii) one of R^2 and $R^{2'}$ is hydrogen and the other is Cl; or

(iii) both R^2 and $R^{2'}$ are hydrogen.

6. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 5, wherein R^3 is selected from hydrogen, halogen, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, C_5-C_6 aryl, C_3-C_6 heteroaryl, or C_2-C_5 heterocyclic amine.

7. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to Claim 6, wherein:

(i) R^3 is hydrogen or Cl;

(ii) R^3 is an optionally substituted 5 or 6 membered heteroaryl;

(iii) R^3 is an optionally substituted 4 to 6 membered heterocycloalkyl; or

(iv) R^3 is an optionally substituted 3 to 5 membered cycloalkyl;

wherein each hetero moiety may include 1 or 2 heteroatoms independently selected from O, S and N; and

wherein said optional substituents are independently selected from 1 or 2 substituents of the group consisting of methyl, F and Cl.

8. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 7, wherein:

(i) R^4 is hydrogen;

(ii) R^4 is F and R^5 and R^6 are each hydrogen;

(iii) R^4 is F and R^5 and R^6 are each hydrogen; or

(iii) R^4, R^5 and R^6 are all hydrogen.

9. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 8, wherein:

(i) R^5 is hydrogen;

(ii) R^5 is F;

(iii) R^5 is a 4 or 5 membered heterocycloalkyl;

(iv) R^5 is C_1-C_3 alkyl;

(v) R^5 is 3, 4 or 5 membered cycloalkyl; or

(vi) R^5 is optionally substituted C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 heterocycloalkyl, C_3-C_6 aryl or C_3-C_6 heteroaryl.

10. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 9, wherein R^5 is selected from hydrogen, F, methyl and pyrrolidine.

11. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 10, wherein:

(i) R^6 is hydrogen;

(ii) R^6 is F or Cl;

(iii) R^6 is an optionally substituted 4 or 5 membered heterocycloalkyl;

(iv) R^6 is an optionally substituted 8, 9 or 10 membered bicyclic or spirocyclic heterocycloalkyl;

(v) R^6 is an optionally substituted 5 or 6 membered heteroaryl;

(vi) R^6 is an optionally substituted 4, 5 or 6 membered cycloalkyl or spirocycloalkyl;

(vii) R^6 is a C_1-C_3 haloalkoxy; or

(viii) R^6 is a C_2-C_8 alkylamine or dialkylamine

wherein each hetero moiety may include 1 or 2 heteroatoms independently selected from O, S and N; and

wherein said optional substituents are independently selected from 1 or 2 substituents from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxyl, F, Cl and hydroxyl.

12. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 11, wherein R^6 is selected from hydrogen, F, methyl and pyrollidine.

13. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 12, wherein L is $-CH_2-$ or $-CH_2-CH_2-$.

14. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 13, wherein Q is selected from the group consisting of optionally substituted 5 to 7 membered heterocycloalkyl and optionally substituted 4 to 7 membered mono or fused or bridged bicycloalkylamine;

wherein each heterocyclic moiety may include 1 or 2 heteroatoms independently selected from O and N; and

wherein said optional substituents are independently selected from 1 to 3 substituents from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxyl, C_1-C_3 alkylamine, C_1-C_3 dialkylamine, C_1-C_3 carbonyl, amine, amino-C_1-C_3 alkyl, oxo, F, Cl and hydroxyl.

15. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 14, wherein:

(i) R^7 is independently selected from C_1-C_3 alkyl, C_1-C_3 haloalkyl, hydroxyl, oxo, F, C_1-C_3 alkylamino, C_1-C_3 dialkylamino or amino; or

(ii) R^7 is independently selected from methyl, ethyl, amine and F;

wherein there are 1, 2 or 3 R^7 groups.

16. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 4, wherein:

(i) R^1 is cyano; and/or

(ii) R^2 and $R^{2'}$ are each independently hydrogen or F; and/or

(iii) R^3 is selected from hydrogen, propyl, i-propyl, CHF_2, cyclopropyl, $-CH_2-$cyclopropyl, $-CH_2-$oxetane, isothiazole, oxazole, fluorooxazole, pyridyl, methoxyl, $-O-CH_2-$

cyclopropyl, -O-CH_2-CF_3, -O-CF_3, CF_3, Cl, amino, - N(CH_3)(CH_2-isopropyl), pyrrolidine, and cyano; and/or

(iv) R^4 is hydrogen or F; and/or

(v) R^5 is selected from hydrogen, methyl, cyclopropyl, cyclopentenyl, F, amino, and NH-CH_2-CH_2-N(CH_3)$_2$; and/or

(vi) R^6 is selected from hydrogen, -O-cyclobutyl, -O-CH_2-oxane, -O-CH_2-CH_2-CHF_2, -O-CH_2-CH_2-CF_3, -O-CH_2-CF_3, -CH_2-O-CHF_2, amino, -N(CH_3)(CH-(CH_3)$_2$, benzimdazole, and pyridine; and/or

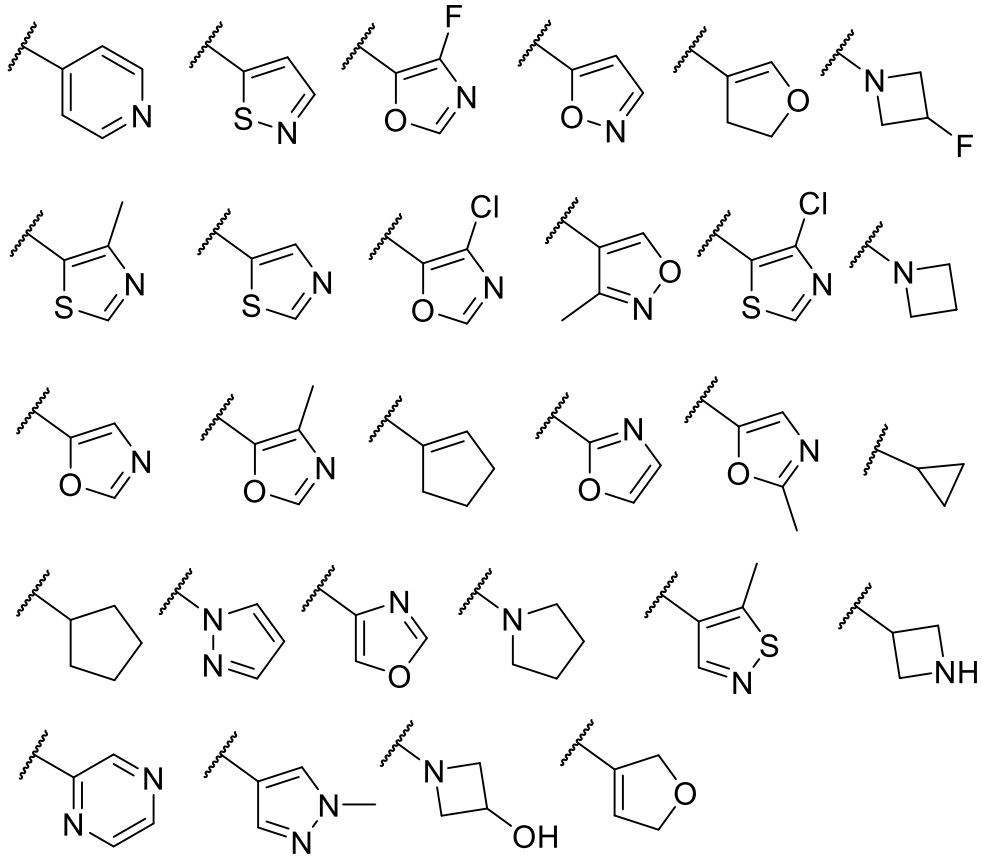
(vii) L is a linker selected from a bond, -CH_2-, -C≡C-, and -CH_2-NH-CH_2-, and/or

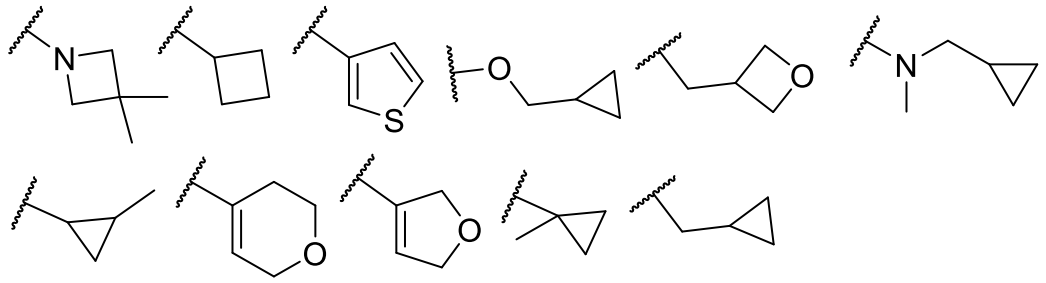
(viii) Q is C_4-C_8 heterocycloalkyl which may comprise a further heteroatom selected from N and O; or Q is morpholinyl; and wherein

each heteroaryl, heterocycloalkyl and/or cycloalkyl group is optionally substituted.

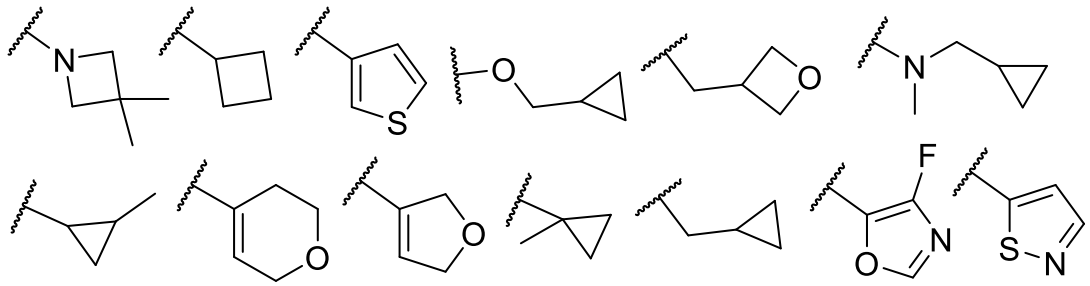
17. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to Claim 16, wherein each heteroaryl, heterocycloalkyl and/or cycloalkyl group is optionally substituted with one or more groups selected from F, Cl, methyl, hydroxyl and amino.

18. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 17, wherein R^3 is selected from the group consisting of the following structures:

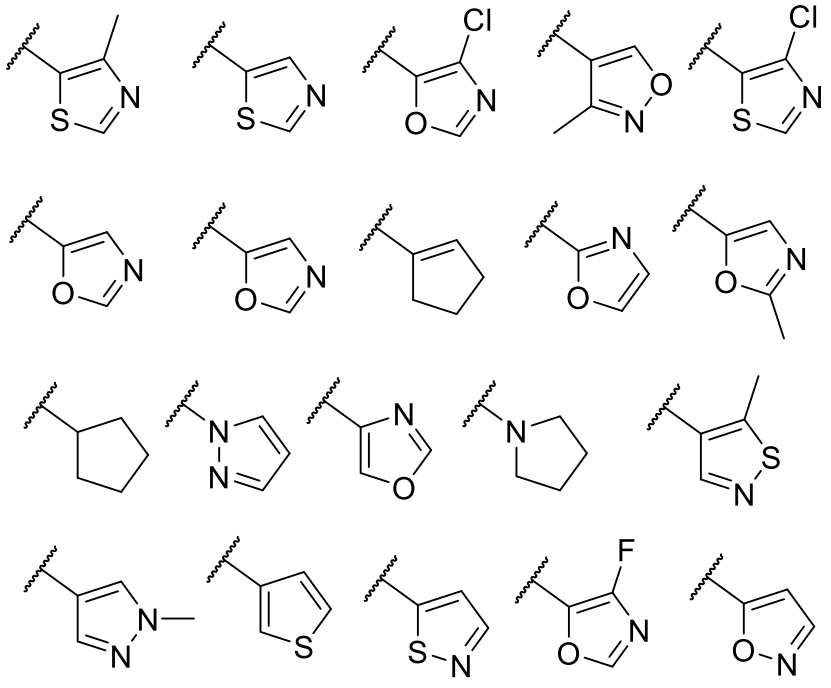




19. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 18, wherein R^3 is selected from the group consisting of the following structures:

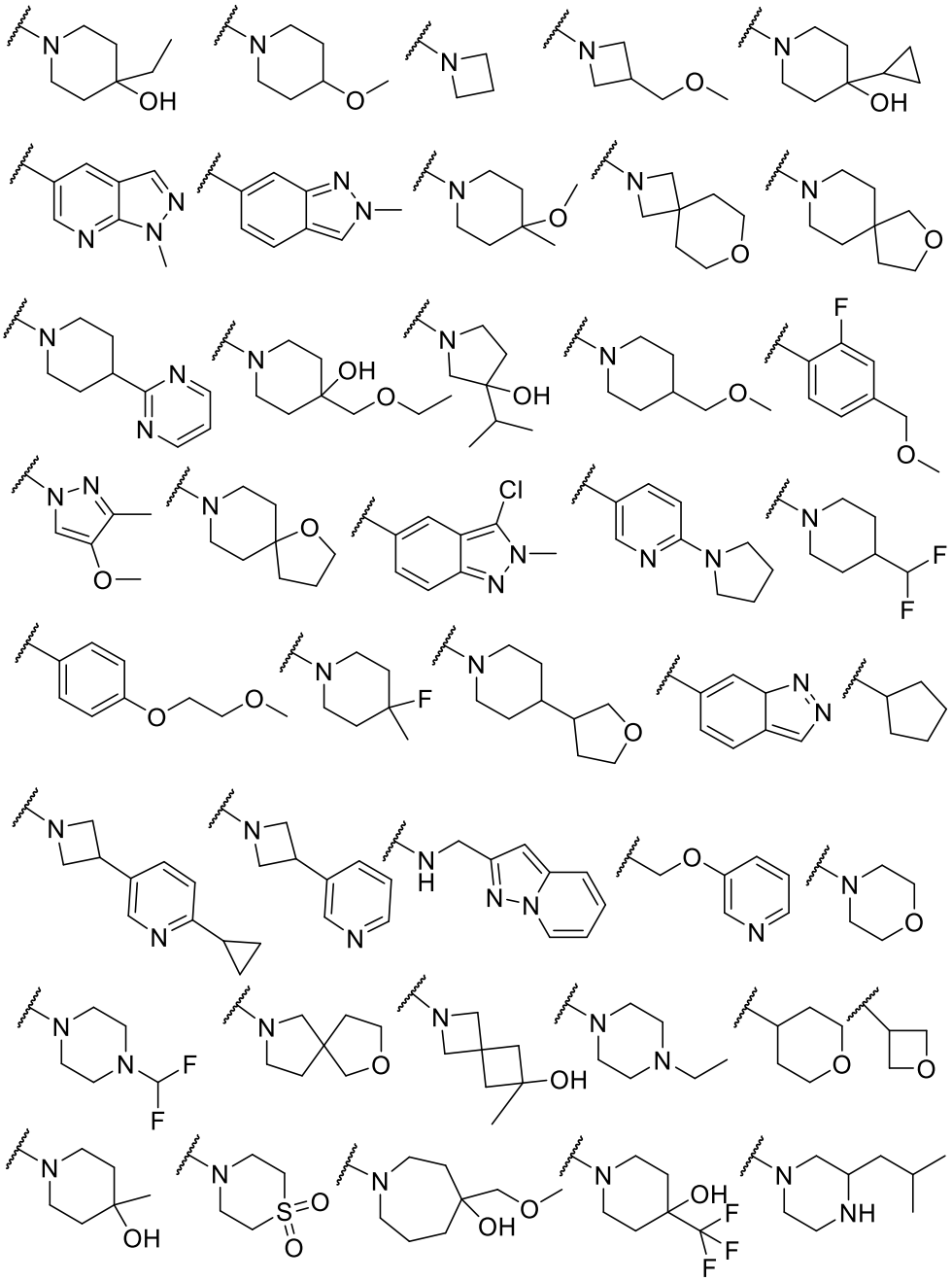


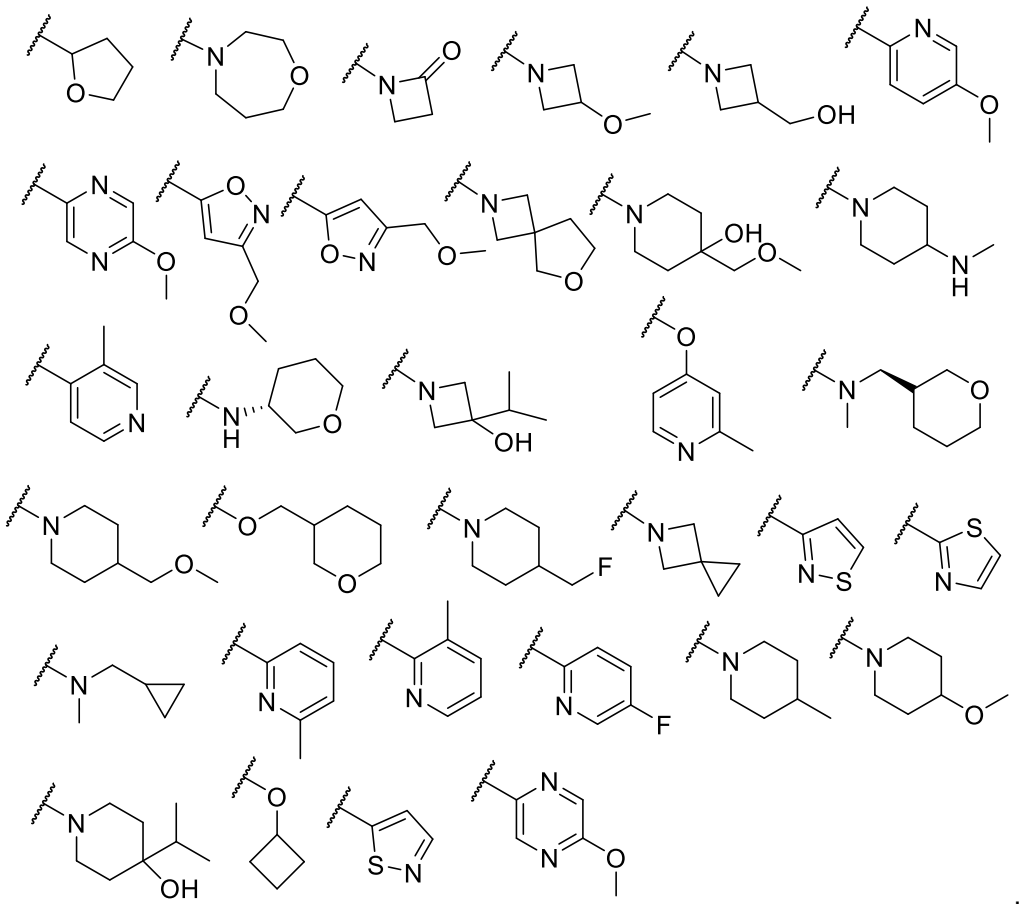
20. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 19, wherein R^5 is selected from the group consisting of hydrogen and the following structures:



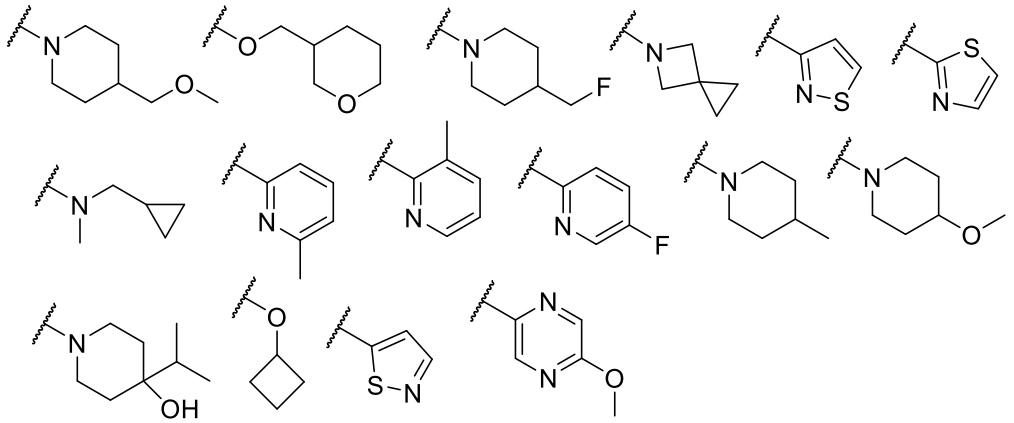
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21. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 20, wherein R^6 is selected from the group consisting of hydrogen and the following structures:

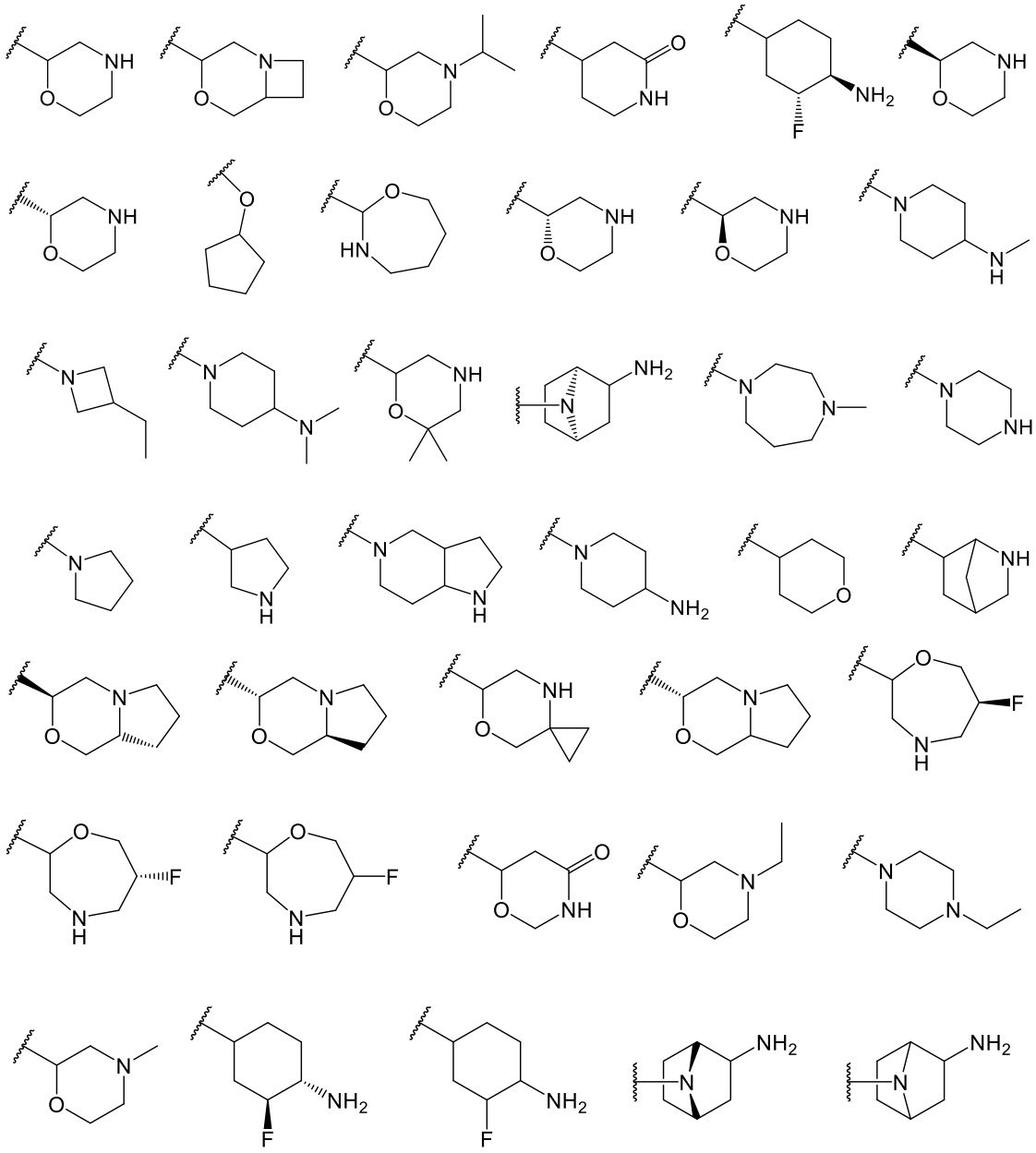


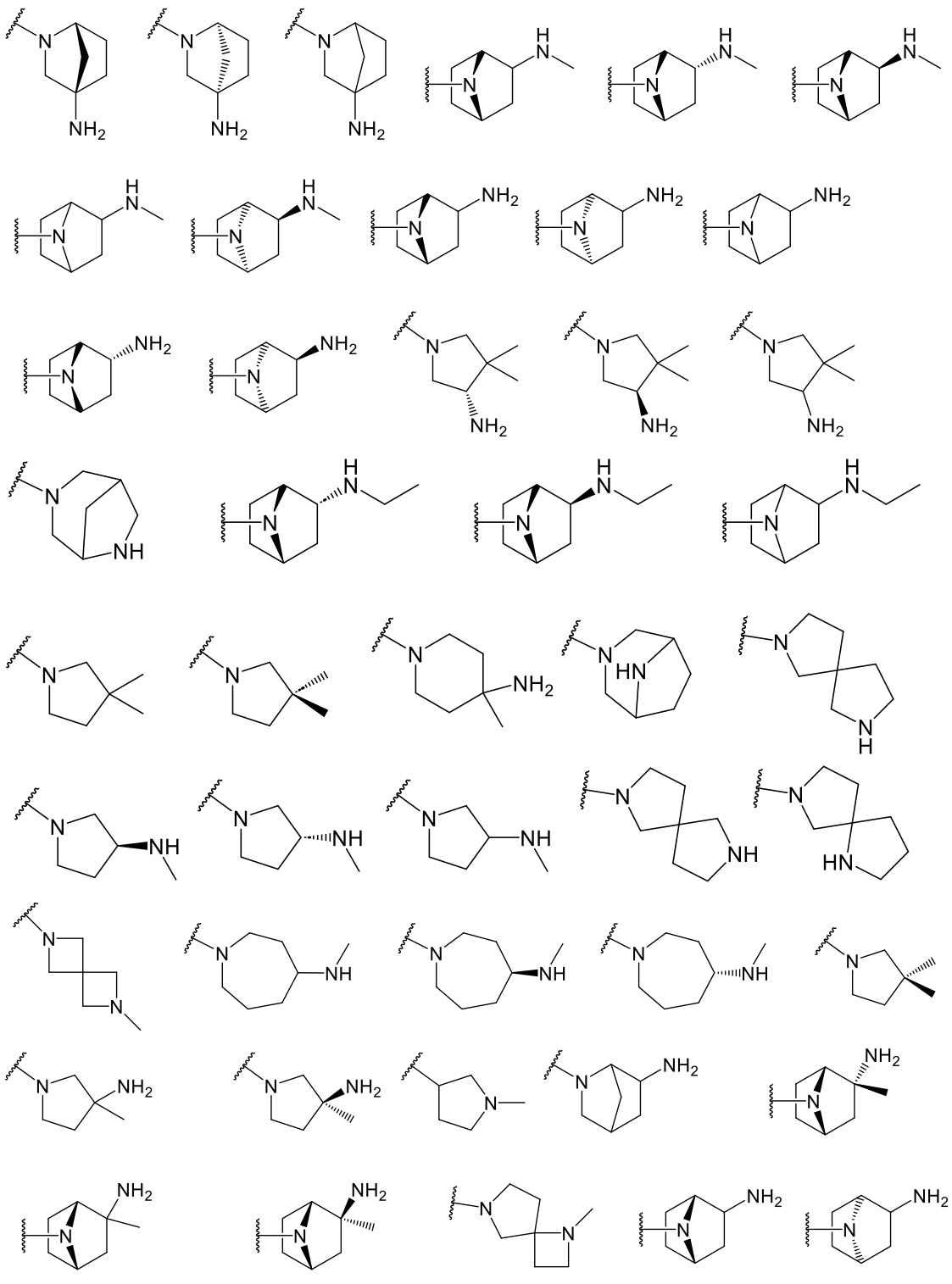


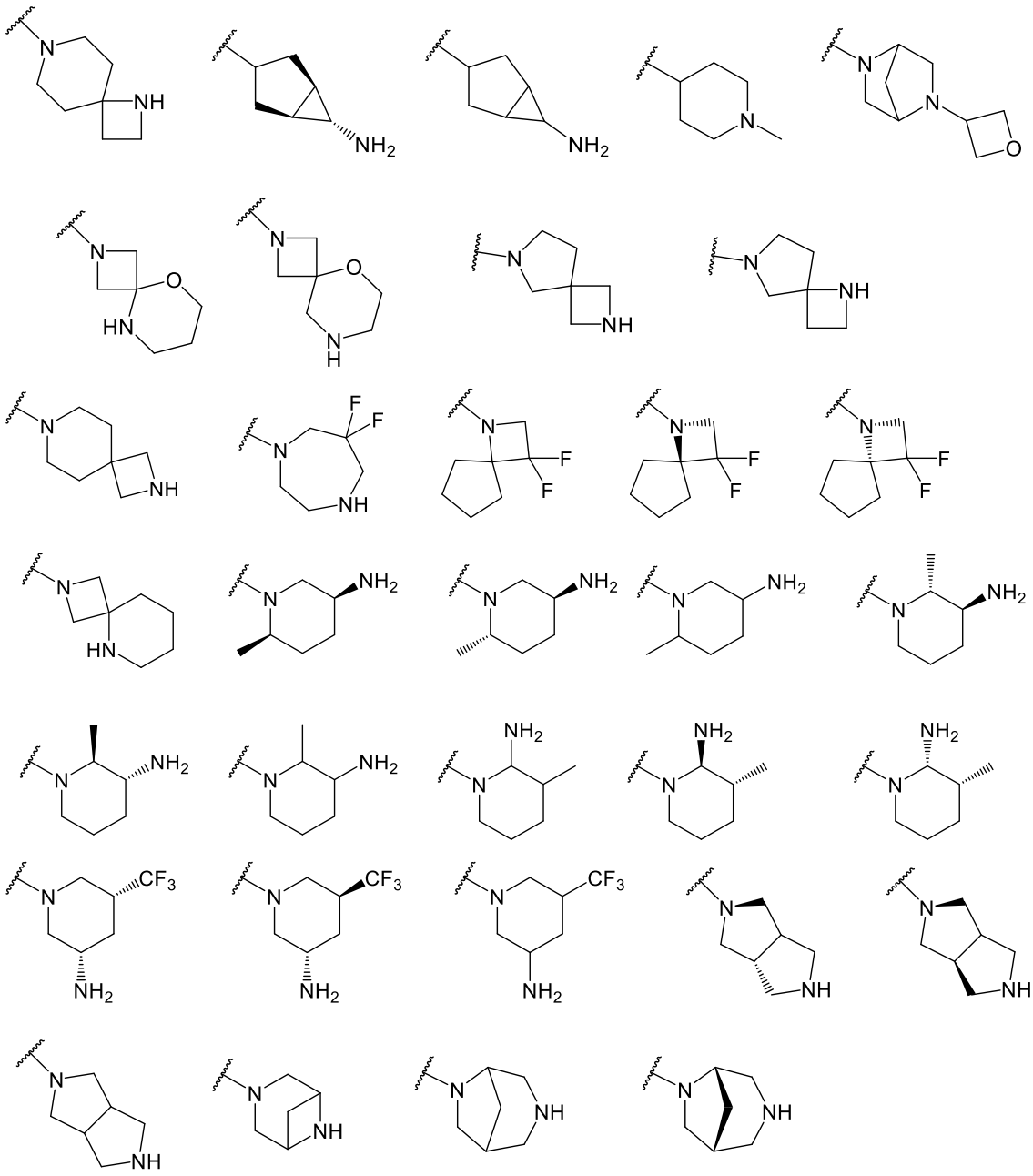
22. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 21, wherein R^6 is selected from the group consisting of hydrogen and the following structures:

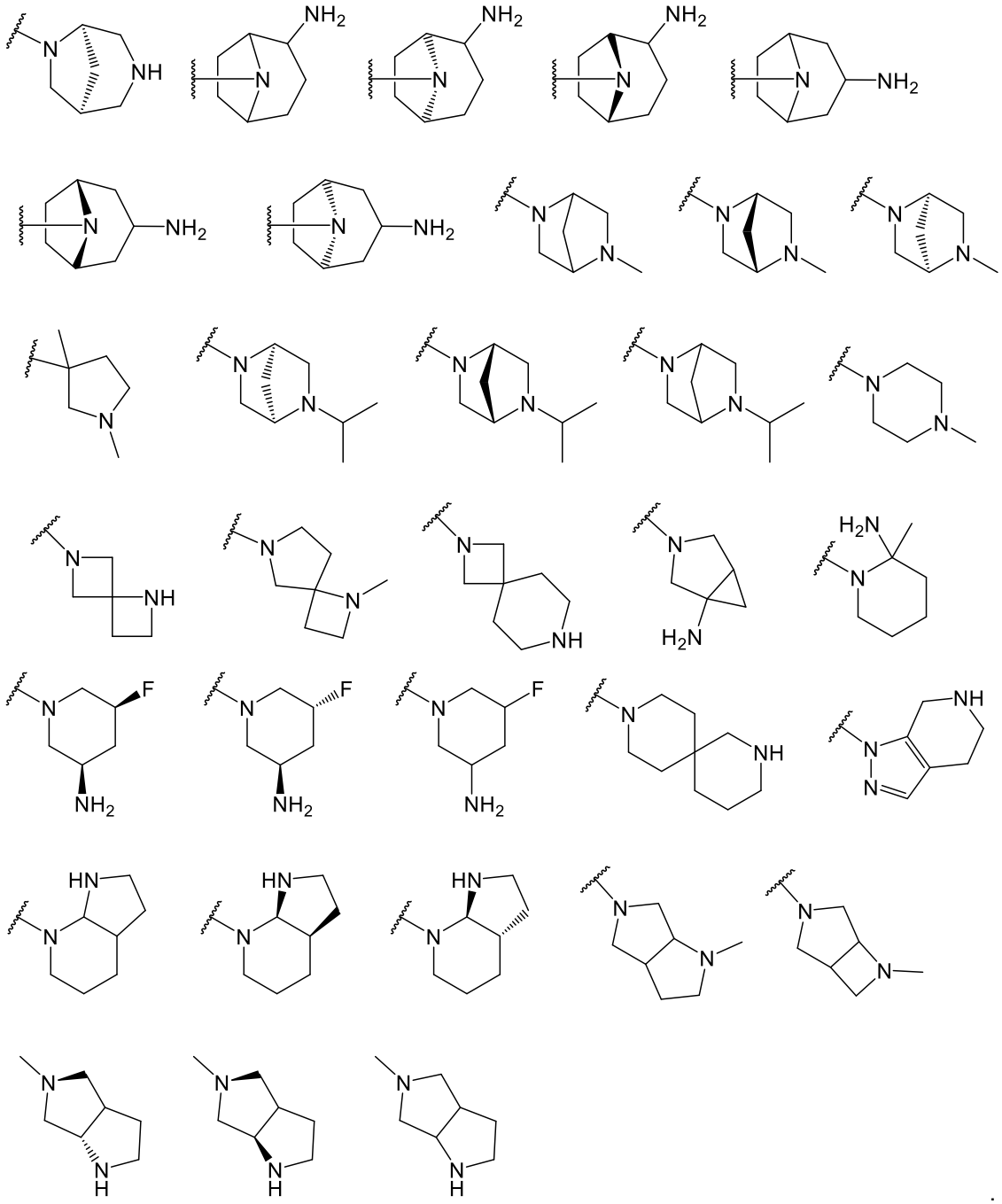


23. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 22, wherein Q is selected from the group consisting of the following structures:

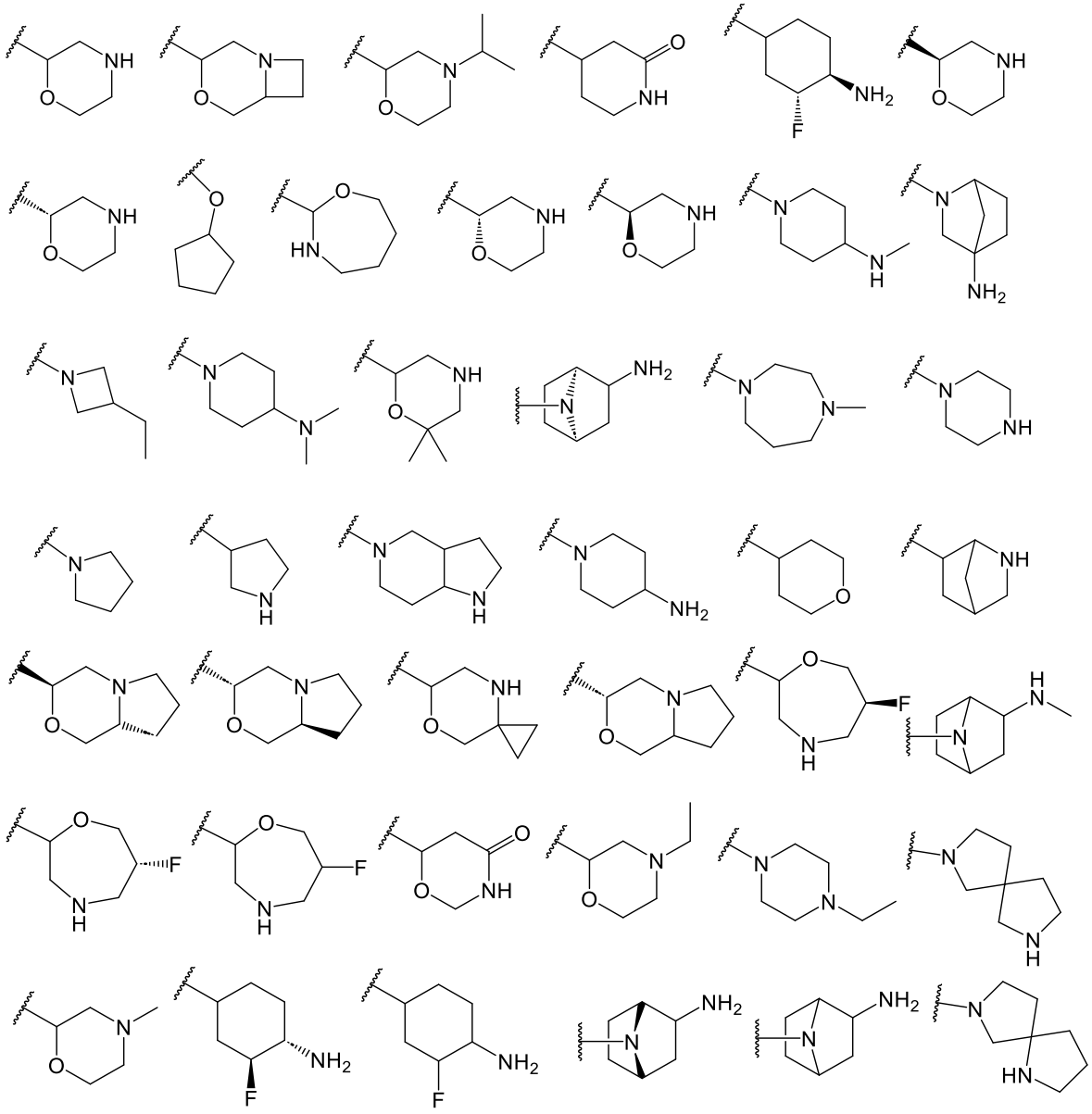






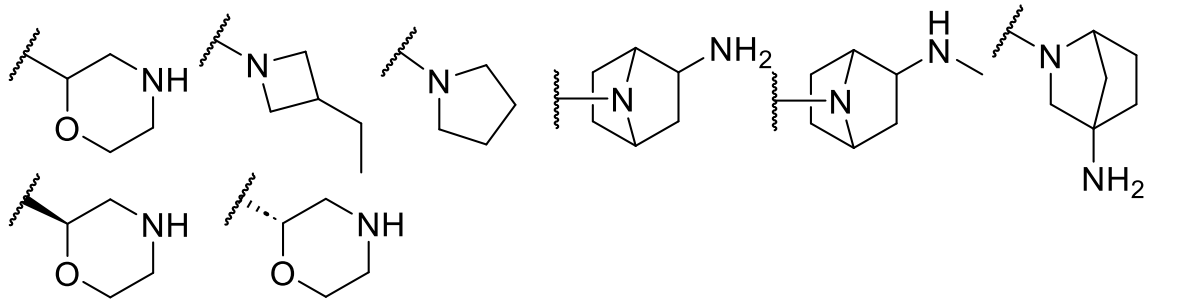


24. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 23, wherein Q is selected from the group consisting of the following structures:



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25. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any of Claims 1 to 24, wherein Q is selected from the group consisting of the following structures:



.

26. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to Claims 1 to 4, wherein:

(i) R^1 is cyano; and/or

(ii) R^2 and $R^{2'}$ are each independently hydrogen or F; and/or

(iii) R^3 is selected from hydrogen, isothiazole, oxazole, fluorooxazole, and pyridyl; and/or

(iv) R^4 is hydrogen or F; and/or

(v) R^5 is hydrogen, methyl, or F; and/or

(vi) R^6 is hydrogen, -O-cyclobutyl, or -O-CH_2-oxane; and/or

(vii) L is a linker selected from a bond, -CH_2-, and -C≡C-; and/or

(viii) Q is C_4-C_8 heterocycloalkyl which may comprise a further heteroatom selected from N or O; or Q is morpholinyl; and wherein

each heteroaryl, heterocycloalkyl and/or cycloalkyl group is optionally substituted.

27. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to Claims 1 to 4, wherein:

(i) R^1 is cyano, and/or

(ii) one of R^2 and $R^{2'}$ is hydrogen and the other is F, and/or

(iii) R^3 is thiazole, or R^3 is 1,2-thiazole, and/or

(iv) R^4, R^5 and R^6 are each hydrogen, and/or

(v) L is -CH2-, and/or

(vi) Q is morpholine.

28. A compound selected from any one of:

(i) the group of compounds shown in Table 1;

(ii) the group of compounds of Table 1 having an IC50 against LSD1 ≤ 1,000 nM;

(iii) the group of compounds of Table 1 having an IC50 against LSD1 ≤ 250 nM;

(iv) the group of compounds of Table 1 having an IC50 against LSD1 ≤ 100 nM;

(v) the group of compounds of Table 1 having an IC50 against LSD1 ≤ 50 nM;

(vi) the group of compounds of Table 1 having an IC50 against LSD1 ≤ 25 nM; or

(vii) the group of compounds of Table 1 having an IC50 against LSD1 ≤ 10 nM;

or a pharmaceutically acceptable salt thereof.

29. A compound selected from any one of Examples 1 to 351.

30. A pharmaceutical composition comprising a compound according to any of Claims 1 to 29 or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier.

31. The compound according to any of Claims 1 to 29, or the pharmaceutical composition according to Claim 30, for use in medicine.

32. Use of a compound according to any one of claims 1 to 29, or the pharmaceutical composition according to Claim 30, in the manufacture of a medicament for the treatment of diseases, conditions or disorders associated with LSD1.

33. Use of a compound according to any one of claims 1 to 29, or the pharmaceutical composition according to Claim 30, in the manufacture of a medicament for the treatment of cancers, oncologic diseases, autoimmune disorders and/or inflammatory diseases.

34. The use according to Claim 32 or 33, wherein the use is in the treatment of diseases, conditions or disorders selected from the group consisting of: breast, prostate, head and neck, brain, laryngeal, oral and thyroid cancers (e.g. papillary thyroid carcinoma), hematological cancers (e.g. non-Hodgkin lymphoma, B cell lymphoma; chronic myelogenous leukemia), sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers and skin cancers.

35. The use according to any of Claims 32 to 34, wherein the use is in the treatment of diseases, conditions or disorders selected from the group consisting of: glioblastoma, acute myeloid leukemia (AML) and small cell lung cancer (SCLC).

36. The use according to any of Claims 32 to 35, wherein the compound or the pharmaceutical composition is to be administered to a subject in combination with one or more additional therapeutic agents.