

LSD1 INHIBITORS

CROSS REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/272,082, filed December 29, 2015, and U.S. Provisional Application No. 62/295,369, filed February 15, 2016, the entire content of each application is hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds that inhibit lysine-specific demethylase one (LSD1). In particular, the present invention relates to compounds that irreversibly inhibit the activity of LSD1, pharmaceutical compositions comprising the compounds and methods of use therefor.

BACKGROUND OF THE INVENTION

[0003] Lysine-specific demethylase one ("LSD1"), also known as KDM1A, is a flavin-dependent lysine demethylase that removes methyl groups from mono- and dimethylated lysine4 of the histone H3 protein through flavin adenine dinucleotide (FAD) dependent enzymatic oxidation (*e.g.*, see Shi et al., (2004) *Cell* 119:941-953). In addition, LSD1 demethylates mono- and dimethylation of histone H3 lysine9 in prostate cancer cell lines and is essential for transcriptional regulation mediated by the androgen receptor (Metzger et al., *Nature* (2005) 437:436-439). LSD1 also demethylates a number of cellular proteins, such as p53, E2F1 and STAT3 and regulates their function.

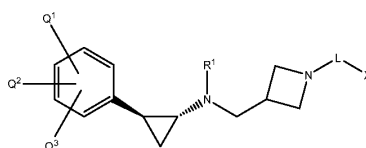
[0004] LSD1 has been reported to be overexpressed in a wide variety of cancers and tissues, including lung cancer, bladder cancer, neuroblastoma, prostate cancer and breast cancer. LSD1 is thought to play a role in cellular proliferation and cancer cell growth by modulating prosurvival gene expression and p53 transcriptional activity (*e.g.*, see Suzuki and Miyata (2011) *J. Med. Chem.* 54:8236-8250). LSD1 also plays a role in regulating viral gene transcription, *e.g.*, Herpes Simplex Virus (HSV), by demethylating histone H3 lysine9 required for viral gene expression in the host.

[0005] With increasing evidence that LSD1 plays a critical role in a diverse set of cancers and diseases, a variety of LSD1 inhibitors, including irreversible LSD1 inhibitors, have been reported and are in clinical development. Irreversible cyclopropyl amine-containing inhibitors, *e.g.*, reviewed in Suzuki and Miyata, *ibid*, have been shown to be potent inhibitors of the LSD1 enzyme; however, such compounds tend to lack robust cellular potency, have poor metabolic stability and high clearance in vivo.

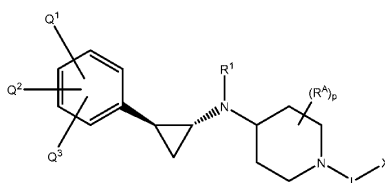
SUMMARY OF THE INVENTION

[0006] The present inventors recognized a need to develop new LSD1 inhibitors that demonstrate improved cellular potency, efficacy, stability and safety. The compounds and compositions of the present invention advantageously overcome one or more of these shortcomings by providing potent, selective and orally active LSD1 inhibitors.

[0007] In one aspect of the invention, compounds are provided that irreversibly inhibit LSD1 activity. In certain embodiments, the compounds are represented by formula (I):



Formula (I)



Formula (II)

[0008] or a pharmaceutically acceptable salt thereof,

[0009] R¹ is hydrogen, C₁-C₄ alkyl or C₁-C₄ acyl;

[0010] L is $-(CH_2)_s-CR^2R^3-(CH_2)_m-$;

[0001] R² and R³ are each independently hydrogen, C₁-C₄ alkyl, $-OR^4$ or aralkyl;

[0002] each R⁴ is independently hydrogen or C₁-C₄ alkyl;

[0003] X is $-W-R^5$ or $Y-R^6$;

[0004] W is $-NR^4-$ or $-O-$;

[0005] Y is $-C(O)-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^4SO_2-$, $-SO_2NR^4-$ and $-NR^4C(O)-$;

[0006] R⁵ is selected from the group consisting of acyl, C₁-C₄alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally independently substituted with one or more R⁸;

[0007] R⁶ is C₁-C₆ alkyl, $-NR^4R^7$ or heterocyclyl optionally independently substituted on one or more carbon atoms with C₁-C₆ alkyl, halogen, cyano, or haloalkyl, or optionally independently substituted on one or more nitrogen atoms with $-C(O)C_1-C_6$ alkyl; $-C(O)OC_1-C_6$ alkyl; $-C(O)NR^4C_1-C_6$ alkyl, or $-S(O)_2NR^4C_1-C_6$ alkyl;

[0008] R^7 is hydroxyl, alkoxy, $-\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl}$; $-\text{SO}_2\text{cycloalkyl}$, or $-\text{SO}_2\text{aryl}$, wherein the cycloalkyl and aryl of each of the $-\text{SO}_2\text{cycloalkyl}$ and $-\text{SO}_2\text{aryl}$ is optionally independently substituted with one or more R^8 ;

[0009] each R^8 is independently halogen, hydroxyl, amino, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, haloalkyl, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, $-(\text{CH}_2)_n\text{COOR}^4$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^4\text{OC}_1\text{-C}_6\text{alkyl}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{cycloalkyl}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{aryl}$, $-\text{C}_2\text{-C}_6$ alkenyl $\text{C}(\text{O})\text{OR}^4$, $-\text{C}_2\text{-C}_6$ alkenyl $\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{C}_1\text{-C}_4\text{alkyl}$, or $-\text{C}_2\text{-C}_6$ alkenyl $\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{aryl}$, wherein each of the cycloalkyl, aryl, heteroaryl, and heterocyclyl is optionally independently substituted with one or more $\text{C}_1\text{-C}_3$ alkyl.

[0010] m is 0 or 1;

[0011] s is 0 or 1;

[0012] each n is 0, 1, or 2;

[0013] each p is 0, 1 or 2;

[0014] each R^A is independently oxo or $\text{C}_1\text{-C}_3$ alkyl, or two R^A groups on different ring atoms together form a $\text{C}_1\text{-C}_3$ bridge in which one of the bridge carbons is optionally replaced with $-\text{NH}-$;

[0015] each Q^1 , Q^2 and Q^3 is independently hydrogen, halogen, haloalkyl, $\text{C}_1\text{-C}_4\text{-alkyl}$, or $\text{C}_1\text{-C}_4\text{-alkoxy}$.

[0016] In another aspect of the invention, pharmaceutical compositions are provided comprising a therapeutically effective amount of a compound of formula (I) or formula (II) and a pharmaceutically acceptable excipient.

[0017] In yet another aspect of the invention, methods for inhibiting LSD1 activity in a cell comprising contacting the cell with a compound of formula (I) or formula (II) are provided. Also provided are methods for treating cancer in a patient comprising administering a therapeutically effective amount of a compound of formula (I) or formula (II) or pharmaceutical composition thereof to a patient in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0018] The present invention relates to LSD1 inhibitors. In particular, the present invention relates to compounds that irreversibly inhibit the activity of LSD1, pharmaceutical compositions comprising a therapeutically effective amount of the compounds, and methods of use therefor.

DEFINITIONS

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, and publications referred to herein are incorporated by reference to the extent they are consistent with the present disclosure. Terms and ranges have their generally defined definition unless expressly defined otherwise.

[0020] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms may also be used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an “alkyl” moiety generally refers to a monovalent radical (*e.g.* CH₃-CH₂-), in certain circumstances a bivalent linking moiety can be “alkyl,” in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH₂-CH₂-), which is equivalent to the term “alkylene.” (Similarly, in circumstances in which a divalent moiety is required and is stated as being “aryl,” those skilled in the art will understand that the term “aryl” refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S).

[0021] As used herein, “LSD1” refers to a mammalian lysine-specific demethylase enzyme (“LSD1”), which removes methyl groups from mono- and dimethylated lysine⁴ and lysine⁹ of the histone H3 protein.

[0022] As used herein, an “LSD1 inhibitor” refers to compounds of the present invention that are represented by formulae (I) or (II) as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of LSD1. The LSD1 inhibitors of the present invention irreversibly inhibit LSD1 activity by forming a covalent adduct with the flavin ring of FAD in the active site of LSD1 following one electron oxidation and cyclopropyl ring opening.

[0023] The term “amino” refers to -NH₂.

[0024] The term “alkyl” as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms. As such, “alkyl” encompasses C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ groups. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[0025] The term “alkenyl” as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms. As such, “alkenyl” encompasses C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ groups.

Examples of alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0026] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms. As such, "alkynyl" encompasses C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ groups. Examples alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0027] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Examples of alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Exemplary alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Exemplary alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0028] The term "alkoxy" refers to -OC₁ - C₆ alkyl.

[0029] The term "alkylthio" refers to -SC₁ - C₆alkyl.

[0030] The term "alkylamino" refers to -NR⁴C₁ - C₆alkyl.

[0031] The term "alkylsulfonyl" refers to -SO₂C₁ - C₆alkyl.

[0032] The term "cycloalkyl" as employed herein is a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons. As such, "cycloalkyl" includes C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂ cyclic hydrocarbon groups. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0033] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are independently replaced O, S, or NR⁴ wherein R⁴ is as defined herein.

[0034] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings. As such, "aryl" includes C₆, C₁₀, C₁₃, and C₁₄ cyclic hydrocarbon groups. An exemplary the aryl group is a C₆-C₁₀ aryl group. Particular aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl.

[0035] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group wherein the moiety is linked to another group via the alkyl moiety. An exemplary aralkyl group is -(C₁- C₆)alkyl(C₆-C₁₀)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0036] A "heterocyclyl" or "heterocyclic" group is a mono- or bicyclic (fused or spiro) ring structure having from 3 to 12 atoms, (3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 atoms), for example 4 to 8 atoms, wherein one or more ring atoms are independently $-C(O)-$, NR^4 , O, or S, and the remainder of the ring atoms are quaternary or carbonyl carbons. Examples of heterocyclic groups include, without limitation, epoxy, azetidiny, aziridiny, tetrahydrofurany, tetrahydropyrany, pyrrolidiny, piperidiny, piperaziny, imidazolidiny, thiazolidiny, dithianyl, trithianyl, dioxolany, oxazolidiny, oxazolidinony, decahydroquinoliny, piperidony, 4-piperidony, thiomorpholiny, dimethyl-morpholiny, and morpholiny. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms.

[0037] The term "heterocyclylalkyl" refers to a heterocyclyl group as defined herein linked to the remaining portion of the molecule via an alkyl linker.

[0038] As used herein, the term "heteroaryl" refers to a group having 5 to 14 ring atoms, preferably 5, 6, 10, 13 or 14 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms that are each independently N, O, or S. "Heteroaryl" also includes fused multicyclic (*e.g.*, bicyclic) ring systems in which one or more of the fused rings is non-aromatic, provided that at least one ring is aromatic and at least one ring contains an N, O, or S ring atom. Examples of such multicyclic heteroaryl ring systems include 2H-benzo[b][1,4]oxazin-3(4H)-one and 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one.

[0039] Examples of heteroaryl groups include acridiny, azociny, benzimidazolyl, benzofurany, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, benzothiofurany, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carboliny, chromany, chromenyl, cinnoliny, furany, furazany, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isobenzofurany, isochromany, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidiny, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperony, pteridiny, puriny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidiny, pyrroliny, 2H-pyrroly, pyrroly, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl,

thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0040] A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to another group via an alkyl linker. Examples of heteroaralkyl groups comprise a C₁-C₆ alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Examples of heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolethyl, thiazolylmethyl, thiazolethyl, benzimidazolylmethyl, benzimidazolethyl, quinazolinylmethyl, quinolinylmethyl, quinolinelethyl, benzofuranyl, indolinylethyl, isoquinolinylmethyl, isoinodolylmethyl, cinnolinylmethyl, and benzothiophenylethyl. Specifically excluded from the scope of this term are compounds having adjacent ring O and/or S atoms.

[0041] An "arylene," "heteroarylene," or "heterocyclylene" group is a bivalent aryl, heteroaryl, or heterocycl group, respectively, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0042] When a hydrocarbon (*e.g.*, an alkyl or aryl) is described as having a certain range of numbers of carbon atoms (*e.g.*, C₁-C₆ alkyl), it will be understood that it encompasses hydrocarbons with each number of carbons within that range. So, for example, "C₁-C₆ alkyl" represents the group "C₁ alkyl, C₂ alkyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl."

[0043] As employed herein, when a moiety (*e.g.*, cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" without expressly stating the substituents it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (*e.g.*, a ring -CH- substituted with oxo is -C(O)-), nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Exemplary substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

[0044] for Q¹, Q² and Q³: hydrogen, halogen, particularly F, Cl or Br, halohydrocarbyl, such as CF₃, alkyl, such as C₁-C₄-alkyl, or alkoxy, such as C₁-C₄-alkoxy.

[0045] A moiety that is "optionally independently substituted" with one or more groups is unsubstituted, substituted with one group, or substituted with more than one group wherein each of the groups is selected independently of the others. For example, an alkyl optionally independently substituted with one or more halo, cyano, or -OH groups includes ethyl, trifluoromethyl, and 1-chloro,2-hydroxypropyl.

[0046] The term "haloalkyl" refers to an alkyl chain in which one or more hydrogens have been replaced by a halogen. Exemplary haloalkyls are trifluoromethyl, difluoromethyl, fluorchloromethyl, and fluoromethyl.

[0047] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine.

[0048] As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent wherein the alkyl and aryl portions are as defined herein. The term "acylamino" refers to an amide group attached at the nitrogen atom (i.e., R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (i.e., NH₂-CO-). The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0049] The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

[0050] As used herein, "an effective amount" of a compound is an amount that is sufficient to to negatively modulate or inhibit the activity of LSD1.

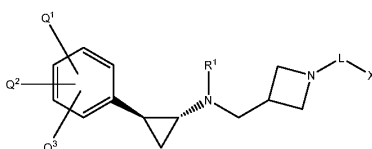
[0051] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of LSD1. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[0052] As used herein, "treatment" means any manner in which the symptoms or pathology of a condition, disorder or disease in a patient are ameliorated or otherwise beneficially altered.

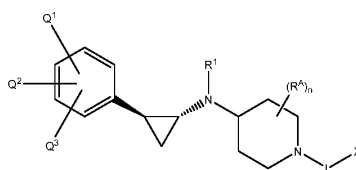
[0053] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient, that can be attributed to or associated with administration of the composition.

COMPOUNDS

[0054] In one aspect of the invention, compounds are provided represented by formula (I) or formula (II):



Formula (I)



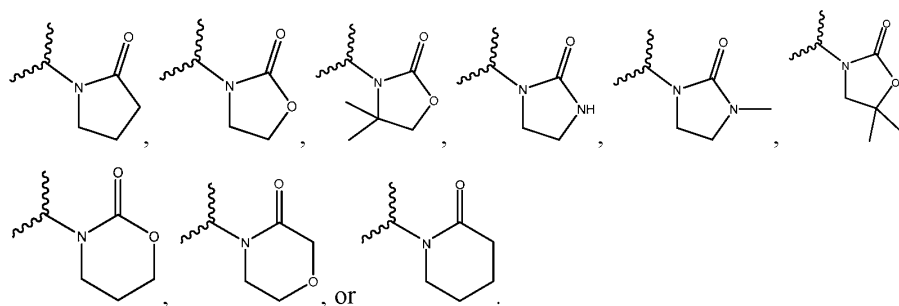
Formula (II)

- [0055] or a pharmaceutically acceptable salts thereof.
- [0056] R^1 is hydrogen, C₁-C₄ alkyl or C₁-C₄ acyl;
- [0057] L is $-(CH_2)_s-CR^2R^3-(CH_2)_m-$;
- [0058] R^2 and R^3 are each independently hydrogen, C₁-C₄ alkyl, $-OR^4$ or aralkyl;
- [0059] each R^4 is independently hydrogen or C₁-C₄ alkyl;
- [0060] X is $-W-R^5$ or $Y-R^6$;
- [0061] W is $-NR^4-$ or $-O-$;
- [0062] Y is $-C(O)-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^4SO_2-$, $-SO_2NR^4-$ and $-NR^4C(O)-$;
- [0063] R^5 is acyl, C₁-C₄ alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally independently substituted with one or more R^8 ;
- [0064] R^6 is C₁-C₆ alkyl, aryl, $-NR^4R^7$ or heterocyclyl optionally independently substituted on one or more carbon atoms with C₁-C₆ alkyl, halogen, cyano, or haloalkyl, or optionally independently substituted on one or more nitrogen atoms with $-C(O)C_1-C_6$ alkyl; $-C(O)OC_1-C_6$ alkyl; $-C(O)NR^4C_1-C_6$ alkyl, or $-S(O)_2NR^4C_1-C_6$ alkyl;
- [0065] R^7 is hydroxyl, alkoxy, $-SO_2C_1-C_6$ alkyl; $-SO_2$ cycloalkyl, or $-SO_2$ aryl, wherein the cycloalkyl and aryl of each of the $-SO_2$ cycloalkyl and $-SO_2$ aryl is optionally independently substituted with one or more R^8 ;
- [0066] each R^8 is independently halogen, hydroxyl, amino, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, haloalkyl, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, $-(CH_2)_nCOOR^4$, $-(CH_2)_nC(O)NR^4OC_1-C_6$ alkyl, $-(CH_2)_nC(O)NR^4SO_2C_1-C_6$ alkyl, $-(CH_2)_nC(O)NR^4SO_2$ cycloalkyl, $-(CH_2)_nC(O)NR^4SO_2$ aryl, $-C_2-C_6$ alkenyl $C(O)OR^4$, $-C_2-C_6$ alkenyl $C(O)NR^4SO_2C_1-C_4$ alkyl, or $-C_2-C_6$ alkenyl $C(O)NR^4SO_2$ aryl, wherein each of the cycloalkyl, aryl, heteroaryl, and heterocyclyl is optionally independently substituted with one or more C₁-C₃ alkyl or $-CH_2NR^4SO_2$ aryl.
- [0067] m is 0 or 1;
- [0068] s is 0 or 1;
- [0069] each n is 0, 1, or 2;
- [0070] each p is 0, 1 or 2;

[0071] each R^A is independently oxo or C₁-C₃ alkyl, or two R^A groups on different ring atoms together form a C₁-C₃ bridge in which one of the bridge carbons is optionally replaced with -NH-;

[0072] each Q^1 , Q^2 and Q^3 is independently hydrogen, halogen, haloalkyl, C₁-C₄-alkyl, or C₁-C₄-alkoxy.

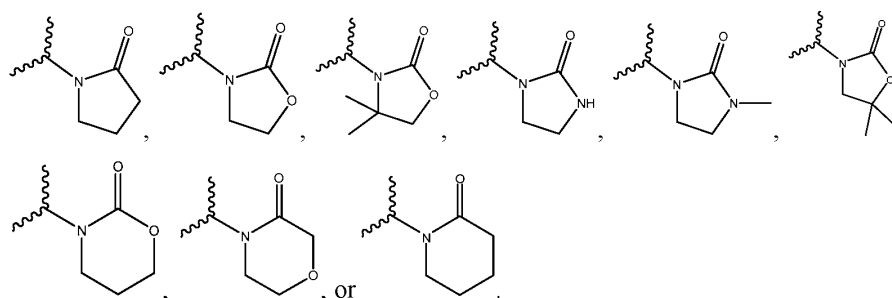
[0073] In one aspect of the invention, X is -W- R^5 and W is -O-, s is 1 and m is 0. In certain embodiments of this aspect, R^5 is aryl optionally independently substituted with one or more R^8 . In some these embodiments, the aryl is phenyl optionally independently substituted with one or more R^8 . In some of these embodiments, each R^8 is independently a heterocyclyl optionally independently substituted one or more C₁-C₃ alkyl or C₁-C₄ acyl, and the heterocyclyl is azetidiny, pyrrolidiny, pyrazolidiny, piperidiny, piperaziny, 4-methyl-piperaziny, 4-acyl-piperaziny, tetrahydropyrany, 1,3-dioxolany, 1,4-dioxany, morpholiny, dimethyl-morpholiny, thiomorpholiny, 1,4-dithiany, or 1,3,5-trithiany. In other of these embodiments, the heterocyclyl is:



[0074] In other embodiments of this aspect, R^5 is phenyl optionally independently substituted with one or more R^8 , wherein each R^8 is independently halogen, C₁ - C₆ alkyl, - $(CH_2)_nCOOR^4$, - $(CH_2)_pC(O)NR^4OC_1-C_4alkyl$, - $(CH_2)_pC(O)NR^4SO_2C_1-C_4alkyl$, - $(CH_2)_nC(O)NR^4SO_2cycloalkyl$, - $(CH_2)_nC(O)NR^4SO_2aryl$, - $CH=CHC(O)OR^4$, - $CH=CHC(O)NR^4SO_2C_1-C_4alkyl$, or - $CH=CHC(O)NR^4SO_2aryl$. In some of these embodiments, there is a single R^8 substitution which is - $(CH_2)_nCOOR^4$.

[0075] In further embodiments of this aspect, R^5 is heteroaryl optionally independently substituted with one or more R^8 . In certain embodiments, the heteroaryl optionally independently substituted with one or more R^8 is the heteroaryl is pyridyl, 6-methyl-pyridyl, 4-carboxy-pyridyl, dihydroquinolinone, indolinone, quinazolinyl, quinoliny, pyrimidinyl, 2-methyl-pyrimidinyl, pyridazinyl, 6-methyl-pyridiazinyl, pyrazolyl, 1-methyl-pyrazolyl, 5-methyl-pyrazolyl, 1,3-dimethyl-pyrazolyl, thiazolyl, 5-methyl-thiazolyl, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, thiadiazolyl or 5-methyl-thiadiazolyl.

[0076] In yet other embodiments, the heteroaryl is pyridyl optionally independently substituted with one or more R^8 . For some of these embodiments, R^8 is heterocyclyl optionally independently substituted with one or more C_1 - C_3 alkyl or C_1 - C_4 acyl. In some embodiments, the heterocyclyl optionally independently substituted with one or more C_1 - C_3 alkyl or C_1 - C_4 acyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, tetrahydropyranyl, 1,3-dioxolanyl, 1,4-dioxanyl, morpholinyl, dimethyl-morpholinyl, thiomorpholinyl, 1,4-dithianyl, or 1,3,5-trithianyl. In other embodiments, the R^8 heterocyclyl is:



In yet other embodiments of this aspect, R^8 is halogen, C_1 - C_6 alkyl, $-(CH_2)_nCOOR^4$, $-(CH_2)_pC(O)NR^4OC_1-C_4alkyl$, $-(CH_2)_pC(O)NR^4SO_2C_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4SO_2cycloalkyl$, $-(CH_2)_nC(O)NR^4SO_2aryl$, $-CH=CHC(O)OR^4$, $-CH=CHC(O)NR^4SO_2C_1-C_4alkyl$, or $-CH=CHC(O)NR^4SO_2aryl$.

[0077] In other embodiments of this aspect for compounds of formula (II), R^A is oxo and n is 1 or 2, thereby forming a piperidin-2-one or piperidin-2,6-dione. In alternative embodiments for compounds of formula (II), there are two R^A groups on different piperidine ring atoms that form a C_1 - C_3 bridge in which one of the carbon atoms of the bridge is optionally substituted by $-NH-$. Examples of piperidine groups with two R^A groups forming a bridge include, but are not limited to, 3-azabicyclo[3.1.1]heptan-3-yl, 1-azabicyclo[2.2.2]octan-3-yl, 1-azabicyclo[2.2.2]octan-4-yl, 1-azabicyclo[3.2.1]octan-6-yl, and 3,7-diazabicyclo[3.3.1]nonanyl.

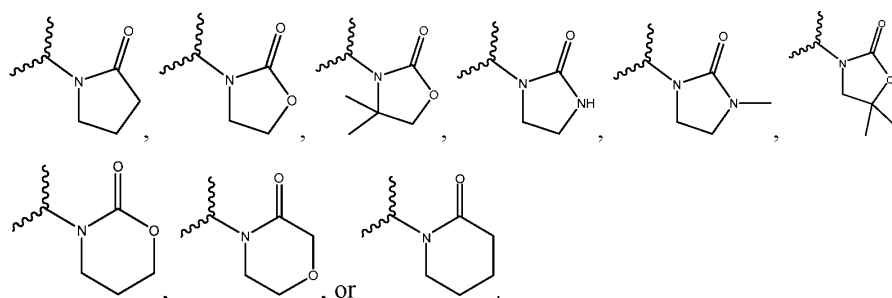
[0078] In certain embodiments of this aspect, R^1 is hydrogen, C_1 - C_4 alkyl or C_1 - C_4 acyl and R^2 and R^3 are each independently hydrogen, C_1 - C_4 alkyl, $-OR^4$ or aralkyl, wherein R^4 is hydrogen or alkyl. In certain embodiments, R^2 is hydroxyl. In certain other embodiments, R^2 and R^3 are each independently hydrogen, methyl and benzyl. In certain other exemplary embodiments, R^4 is hydrogen or methyl.

[0079] In certain other embodiments of this aspect, R^1 is hydrogen, L is ethylene, W is $-O-$, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny,

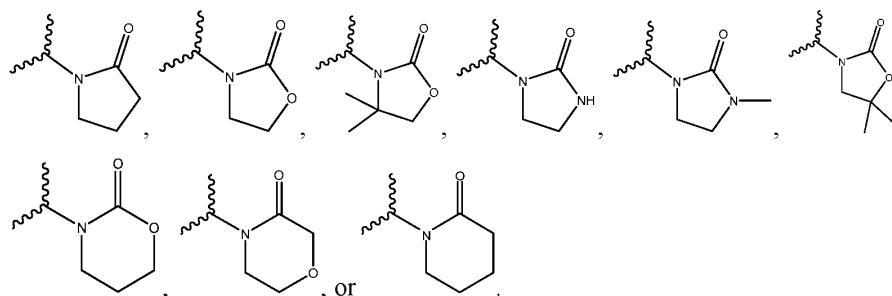
pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.

[0080] In certain other embodiments of this aspect, R^1 is methyl, L is ethylene, W is -O-, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.

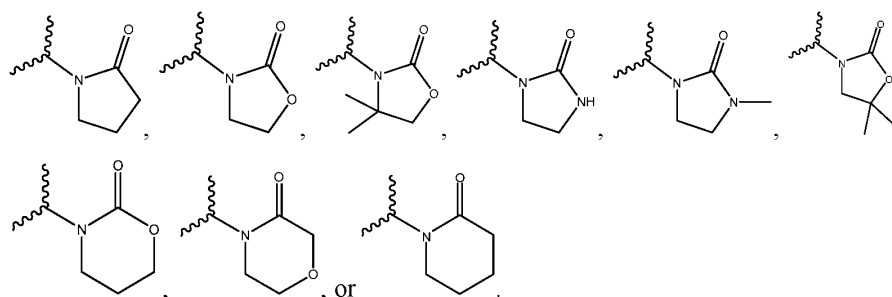
[0081] In certain other embodiments of this aspect, R^1 is hydrogen, L is ethylene, W is -O-, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



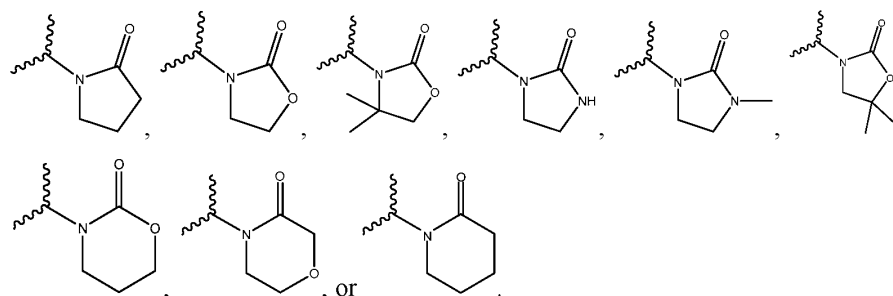
[0082] In certain other embodiments of this aspect, R^1 is methyl, L is ethylene, W is -O-, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



[0083] In certain other embodiments of this aspect, R^1 is acyl, L is ethylene, W is -O-, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



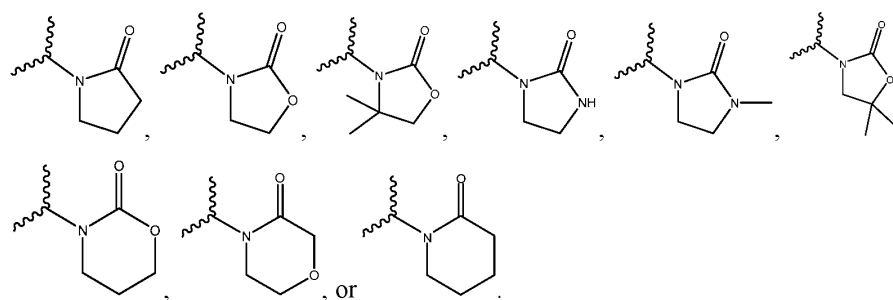
[0084] In another aspect of the invention, R^1 is hydrogen, s and m are each one, R^2 is hydroxyl, R^3 is hydrogen, W is -O-, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



[0085] In yet another aspect of the invention, R^1 is hydrogen, L is ethylene, W is -O-, R^5 is an R^8 substituted pyridylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.

[0086] In certain other embodiments of this aspect, R^1 is methyl, L is ethylene, W is -O-, R^5 is an R^8 substituted pyridylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.

[0087] In certain other embodiments of this aspect, R^1 is hydrogen, L is ethylene, W is -O-, R^5 is an R^8 substituted pyridylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



[0088] In certain embodiments, compounds of formula (I) and formula (II) wherein W is -O- are

[0089] 1-phenoxy-3-[4-[[trans-2-phenylcyclopropyl] amino]-1-piperidyl] propan-2-ol;

[0090] 1-(2-methoxy-3-phenoxy-propyl)-N-[trans-2-phenylcyclopropyl]piperidin-4-amine;

[0091] 2-methyl-1-phenoxy-3-(4-(((trans)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol;

- [0092] 1-phenoxy-3-[3-[[[(*trans*)-2-phenylcyclopropyl]amino]methyl]azetidin-1-yl]propan-2-ol;
- [0093] (*R*)-1-phenoxy-3-(4-(((1*S*,2*R*)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol;
- [0094] (*S*)-1-phenoxy-3-(4-(((1*S*,2*R*)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol;
- [0095] 1-phenoxy-3-[(1*R*,5*S*)-6-[[(*trans*)-2-phenylcyclopropyl]amino]-3-azabicyclo[3.1.1]heptan-3-yl]propan-2-ol;
- [0096] (*trans*)-*N*-[[1-(2-phenoxyethyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine;
- [0097] (*trans*)-*N*-[[1-(3-phenoxypropyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine;
- [0098] 1-[2-(4-bromophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine;
- [0099] 1-(3-Phenoxypropyl)-*N*-((*trans*)-2-phenylcyclopropyl)piperidin-4-amine;
- [0100] 1-(2-Phenoxyethyl)-*N*-((*trans*)-2-phenylcyclopropyl)piperidin-4-amine;
- [0101] 2-(4-(2-(4-(((1*R*,2*S*)-2-Phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;
- [0102] *N*-(Methylsulfonyl)-2-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide;
- [0103] 2-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-*N*-(phenylsulfonyl)acetamide;
- [0104] *N,N*-Dimethyl-2-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide;
- [0105] *N*-methoxy-2-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide;
- [0106] 1-[2-(4-morpholinophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine;
- [0107] 1-(2-(4-(4-methylpiperazin-1-yl)phenoxy)ethyl)-*N*-((1*R*,2*S*)-2-phenylcyclopropyl)piperidin-4-amine;
- [0108] 3-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)oxazolidin-2-one;
- [0109] 1-methyl-3-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)imidazolidin-2-one;
- [0110] 3-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;

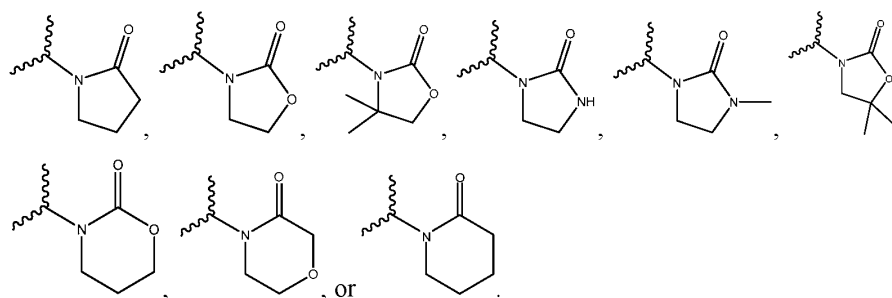
- [0111] 4-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)morpholin-3-one;
- [0112] 1-(4-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)piperazin-1-yl)ethan-1-one;
- [0113] 1-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)pyrrolidin-2-one;
- [0114] 1-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)piperidin-2-one;
- [0115] N-(((1R,2S)-2-phenylcyclopropyl)-1-(2-(4-(piperidin-1-yl)phenoxy)ethyl)piperidin-4-amine;
- [0116] 2-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acetic acid;
- [0117] 4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)benzoic acid;
- [0118] (*E*)-3-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylic acid;
- [0119] 2-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acetic acid;
- [0120] 4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)benzoic acid;
- [0121] (*E*)-3-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylic acid;
- [0122] (1R,2S)-N-((1-(2-(4-bromophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;
- [0123] 1-(2-(2,4-dichlorophenoxy)ethyl)-N-(((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0124] (1R,2S)-N-((1-(2-(2,4-dichlorophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;
- [0125] 1-(2-(2,4-difluorophenoxy)ethyl)-N-(((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0126] (1R,2S)-N-((1-(2-(2,4-difluorophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;
- [0127] (*E*)-3-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)-N-(methylsulfonyl)acrylamide;

- [0128] 1-(2-((2-methylpyridin-4-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0129] (1R,2S)-2-phenyl-N-((1-(2-(p-tolyl)oxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine;
- [0130] (1R,2S)-2-phenyl-N-((1-(2-(pyridin-2-yl)oxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine;
- [0131] 4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzoic acid;
- [0132] N-(cyclopropylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide;
- [0133] 4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-N-(phenylsulfonyl)benzamide;
- [0134] (E)-N-(methylsulfonyl)-3-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylamide;
- [0135] 3-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;
- [0136] 4-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)morpholin-3-one
- [0137] 1-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)piperidin-2-one;
- [0138] (1R,2S)-2-phenyl-N-((1-(2-(4-(piperazin-1-yl)phenoxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine;
- [0139] (1R,2S)-N-((1-(2-(4-(4-methylpiperazin-1-yl)phenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;
- [0140] 1-(4-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)piperazin-1-yl)ethan-1-one;
- [0141] 1-(2-((5-methylpyridin-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0142] 1-(2-((6-methylpyridin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0143] N-(methylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide;
- [0144] N-(ethylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide;

- [0145] (1S,2R)-N-((1-(2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)oxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;
- [0146] 2-(4-(2-(3-(((1S,2R)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)acetic acid;
- [0147] 4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)benzoic acid
- [0148] 2-(4'-(2-(3-(((1S,2R)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)-[1,1'-biphenyl]-4-yl)-N-(phenylsulfonyl)acetamide;
- [0149] 3-(6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)pyridin-3-yl)-1,3-oxazinan-2-one;
- [0150] 3-(5-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)pyridin-2-yl)-1,3-oxazinan-2-one;
- [0151] N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(p-tolyl)oxy)ethyl)piperidin-4-amine;
- [0152] 3-(4-(2-(4-(methyl((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;
- [0153] 2-(4-(2-(1-methyl-3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)-λ4-azetidin-1-yl)ethoxy)phenyl)-N-(methylsulfonyl)acetamide;
- [0154] N-methyl-1-(2-((6-methylpyridin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0155] (1R,2S)-N-((1-(2-((6-methylpyridin-3-yl)oxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;
- [0156] 4-(2-(1-methyl-3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)-λ4-azetidin-1-yl)ethoxy)-N-(methylsulfonyl)benzamide;
- [0157] 3-(5-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)pyridin-2-yl)-1,3-oxazinan-2-one;
- [0158] 6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-3,4-dihydroquinolin-2(1H)-one;
- [0159] 5-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)indolin-2-one;
- [0160] 1-(2-(3-fluoro-4-methylphenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0161] N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(quinazolin-4-yloxy)ethyl)piperidin-4-amine;
- [0162] N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(quinolin-4-yloxy)ethyl)piperidin-4-amine;
- [0163] N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(pyrimidin-5-yloxy)ethyl)piperidin-4-amine;

- [0164] 1-(2-(3,5-difluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0165] 1-(2-(3,5-dichlorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0166] 1-(2-((6-methylpyridazin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0167] (E)-3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acrylic acid;
- [0168] 1-(2-(3-fluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0169] 1-(2-((6-methylpyridin-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0170] 1-(2-((2-methylpyrimidin-5-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0171] 1-(2-(4-bromophenoxy)ethyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-2-one;
- [0172] 2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethan-1-ol;
- [0173] N-(1-(2-(4-(2-oxo-1,3-oxazinan-3-yl)phenoxy)ethyl)piperidin-4-yl)-N-((1R,2S)-2-phenylcyclopropyl)acetamide;
- [0174] 1-(2-methoxyethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0175] 1-(2-(((1,3-dimethyl-1H-pyrazol-5-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0176] 1-(2-((1-methyl-1H-pyrazol-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0177] 3-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;
- [0178] 1-(2-isopropoxyethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0179] 2-(2-fluoro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;
- [0180] 1-(2-(3,5-difluoro-4-methylphenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0181] 1-(2-((5-methyl-1,3,4-thiadiazol-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0182] 2-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)isonicotinic acid;

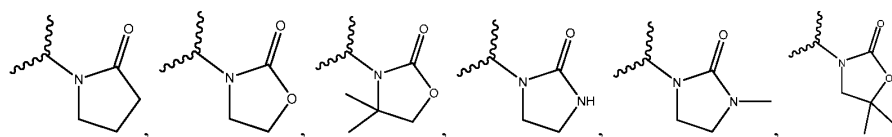
- [0183] 3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)oxazolidin-2-one;
- [0184] 1-(2-(4-bromophenoxy)ethyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidine-2,6-dione;
- [0185] N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(pyridin-3-yloxy)ethyl)piperidin-4-amine;
- [0186] 7-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-2H-benzo[b][1,4]oxazin-3(4H)-one;
- [0187] 6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzo[d]oxazol-2(3H)-one;
- [0188] 1-(2-((5-methylthiazol-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0189] 3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)isonicotinic acid;
- [0190] 2-(3-chloro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;
- [0191] 2-(3-fluoro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;
- [0192] 2-(3-methyl-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;
- [0193] 4-(2-(4-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)piperidin-1-yl)ethoxy)benzoic acid;
- [0194] and pharmaceutically acceptable salts of the foregoing compounds, including, but not limited to, di-hydrochloride salts.
- [0195] In another aspect of the invention, X is -W-R⁵ and W is -NR⁴-, s is 1 and m is 0. In certain embodiments of this aspect, R⁵ is aryl optionally independently substituted with one or more R⁸. In some of these embodiments, the aryl optionally independently substituted with one or more R⁸ is phenyl. In some of these embodiments, each R⁸ is independently a heterocyclyl optionally independently substituted one or more C₁-C₃ alkyl or C₁-C₄ acyl, and the heterocyclyl is azetidiny, pyrrolidiny, pyrazolidiny, piperidiny, piperaziny, 4-methyl-piperaziny, 4-acyl-piperaziny, tetrahydropyrany, 1,3-dioxolany, 1,4-dioxany, morpholiny, dimethyl-morpholiny, thiomorpholiny, 1,4-dithiany, or 1,3,5-trithiany. In other of these embodiments, the heterocyclyl is:

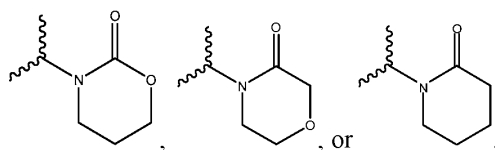


[0196] In other embodiments of this aspect, R^5 is phenyl optionally independently substituted with one or more R^8 , wherein each R^8 is independently halogen, $C_1 - C_6$ alkyl, $-(CH_2)_nCOOR^4$, $-(CH_2)_pC(O)NR^4OC_1-C_4alkyl$, $-(CH_2)_pC(O)NR^4SO_2C_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4SO_2cycloalkyl$, $-(CH_2)_nC(O)NR^4SO_2aryl$, $-CH=CHC(O)OR^4$, $-CH=CHC(O)NR^4SO_2C_1-C_4alkyl$, or $-CH=CHC(O)NR^4SO_2aryl$. In some of these embodiments, there is a single R^8 substitution which is $-(CH_2)_nCOOR^4$.

[0197] In further embodiments where W is $-NR^4$, R^5 is heteroaryl optionally independently substituted with one or more R^8 . In certain embodiments, the heteroaryl optionally independently substituted with one or more R^8 is the heteroaryl is pyridyl, 6-methyl-pyridyl, 4-carboxy-pyridyl, dihydroquinolinone, indolinone, quinazolinyl, quinolinyl, pyrimidinyl, 2-methyl-pyrimidinyl, pyridazinyl, 6-methyl-pyridiazinyl, pyrazolyl, 1-methyl-pyrazolyl, 5-methyl-pyrazolyl, 1,3-dimethyl-pyrazolyl, thiazolyl, 5-methyl-thiazolyl, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, thiadiazolyl or 5-methyl-thiadiazolyl. In yet other embodiments, the heteroaryl is pyridyl optionally independently substituted with one or more R^8 . For certain compounds, R^8 is heterocyclyl optionally independently substituted one or more C_1-C_3 alkyl. In some embodiments, the heterocyclyl optionally independently substituted one or more C_1-C_3 alkyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, tetrahydropyranyl, 1,3-dioxolanyl, 1,4-dioxanyl, morpholinyl, dimethyl-morpholinyl, thiomorpholinyl, 1,4-dithianyl, or 1,3,5-trithianyl.

[0198] In other embodiments, the heterocyclyl optionally independently substituted one or more C_1-C_3 alkyl is





[0199] In yet other embodiments of this aspect, R^5 is pyridyl and each R^8 is independently halogen, alkyl, $-(CH_2)_nCOOR^4$, $-(CH_2)_pC(O)NR^4OC_1-C_4alkyl$, $-(CH_2)_pC(O)NR^4SO_2C_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4SO_2cycloalkyl$, $-(CH_2)_nC(O)NR^4SO_2aryl$, $-CH=CHC(O)OR^4$, $-CH=CHC(O)NR^4SO_2C_1-C_4alkyl$, or $-CH=CHC(O)NR^4SO_2aryl$.

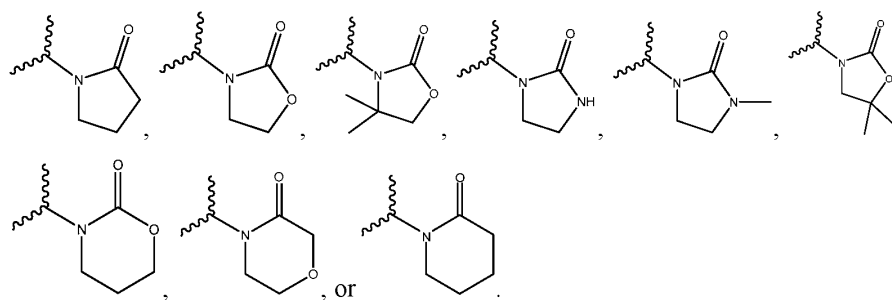
[0200] In other embodiments of this aspect for compounds of formula (II), there are two R^A on the same carbon forming an oxo and n is 1 or 2, thereby forming a piperdin-2-one or piperdin-2,6-dione. In alternative embodiments for compounds of formula (II), there are two R^A groups on different piperidine ring atoms that form a C_1-C_3 bridge in which one of the carbon atoms of the bridge is optionally substituted by $-NH-$. Examples of piperidine groups with two R^A groups forming a bridge include, but are not limited to, 3-azabicyclo[3.1.1]heptan-3-yl, 1-azabicyclo[2.2.2]octan-3-yl, 1-azabicyclo[2.2.2]octan-4-yl, 1-azabicyclo[3.2.1]octan-6-yl, and 3,7-diazabicyclo[3.3.1]nonanyl.

[0201] In certain embodiments of this aspect, R^1 is hydrogen, C_1-C_4 alkyl or C_1-C_4 acyl and R^2 and R^3 are each independently hydrogen, C_1-C_4 alkyl, $-OR^4$ or aralkyl, wherein R^4 is hydrogen or alkyl. In certain embodiments, R^2 is hydroxyl. In certain other embodiments, R^2 and R^3 are each independently hydrogen, methyl and benzyl. In certain other exemplary embodiments, R^4 is hydrogen or methyl.

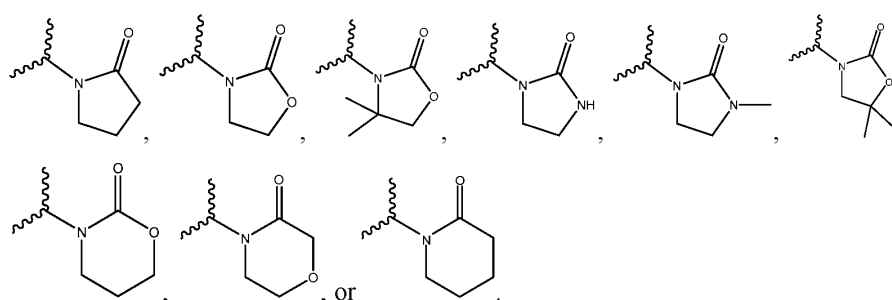
[0202] In certain other embodiments of this aspect, R^1 is hydrogen, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.

[0203] In certain other embodiments of this aspect, R^1 is methyl, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.

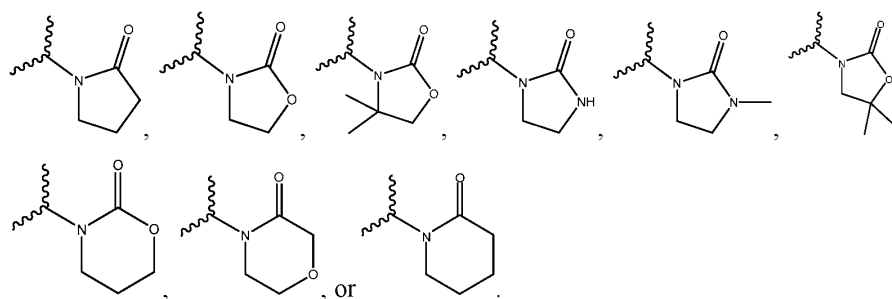
[0204] In certain other embodiments of this aspect, R^1 is hydrogen, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



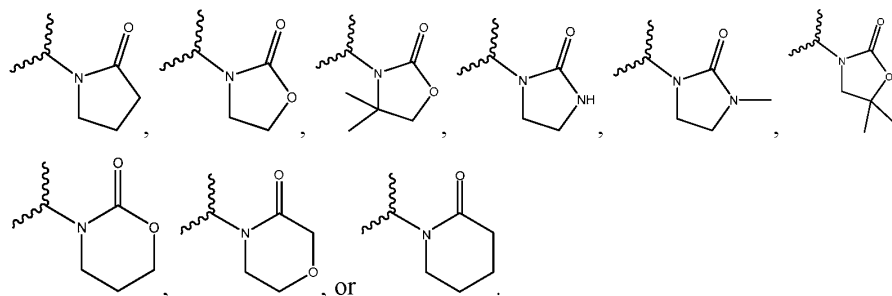
[0205] In certain other embodiments of this aspect, R^1 is methyl, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



[0206] In certain other embodiments of this aspect, R^1 is acyl, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



[0207] In another aspect of the invention, R^1 is hydrogen, s and m are each one, R^2 is hydroxyl, R^3 is hydrogen, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted phenylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:

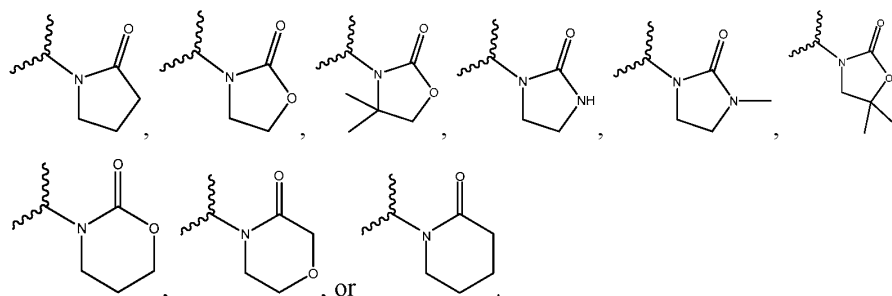


[0208] In certain other embodiments of this aspect, R^1 is hydrogen, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted phenylene, and R^8 is heteroaryl, wherein the heteroaryl is pyridyl, dihydroquinolinone, indolinone, quinazolinyl, quinolinyl, pyrimidinyl, pyridazinyl, pyrazolyl, pyrazolyl, 1-methyl-pyrazolyl, 5-methyl-pyrazolyl, thiazolyl, benzo[d]oxazolone, thiazolyl or 5-methyl-thiazolyl.

[0209] In yet another aspect of the invention, R^1 is hydrogen, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted pyridylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.

[0210] In certain other embodiments of this aspect, R^1 is methyl, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted pyridylene, and R^8 is heterocyclyl, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl or thiomorpholinyl.

[0211] In certain other embodiments of this aspect, R^1 is hydrogen, L is ethylene, W is $-NR^4-$, R^4 is hydrogen, R^5 is an R^8 substituted pyridylene, and R^8 is heterocyclyl, wherein the heterocyclyl is:



[0212] In certain embodiments, compounds of formula (I) and formula (II) wherein W is $-NR^4-$ are:

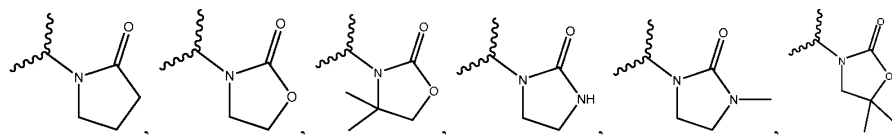
[0213] 1-anilino-3-[4-[[trans-2-phenylcyclopropyl]amino]-1-piperidyl] propan-2-ol;

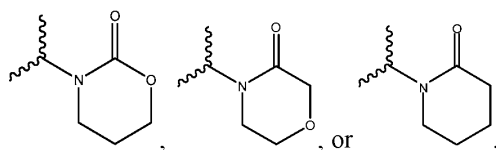
- [0214] 1-(N-methylanilino)-3-[4-[[trans-2-phenylcyclopropyl]amino]-1-piperidyl]propan-2-ol;
- [0215] 1-(2-(phenylamino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0216] 1-(2-(methyl(phenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0217] 1-(2-((4-bromophenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0218] 1-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)piperidin-2-one;
- [0219] 3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one;
- [0220] 4-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)morpholin-3-one;
- [0221] N-((1R,2S)-2-phenylcyclopropyl)-1-(2-((4-(piperidin-1-yl)phenyl)amino)ethyl)piperidin-4-amine;
- [0222] 1-(2-((4-morpholinophenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0223] 1-(2-((4-(4-methylpiperazin-1-yl)phenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0224] 1-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)pyrrolidin-2-one;
- [0225] 3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)oxazolidin-2-one;
- [0226] 1-methyl-3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)imidazolidin-2-one;
- [0227] 1-(4-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)piperazin-1-yl)ethan-1-one;
- [0228] 3-(4-((2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one;
- [0229] N,6-dimethyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)pyridin-3-amine;
- [0230] 1-(2-((4-bromophenyl)(methyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

- [0231] 3-(4-(methyl(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one;
- [0232] 1-methyl-3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)urea;
- [0233] N-methyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)acetamide;
- [0234] N,2-dimethyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)pyridin-4-amine;
- [0235] 1-(2-(4-bromo-2-fluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
- [0236] 2-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)isonicotinic acid; and
- [0237] 3-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)isonicotinic acid.
- [0238] and pharmaceutically acceptable salts of the foregoing compounds, including, but not limited to dihydrochloride salts.

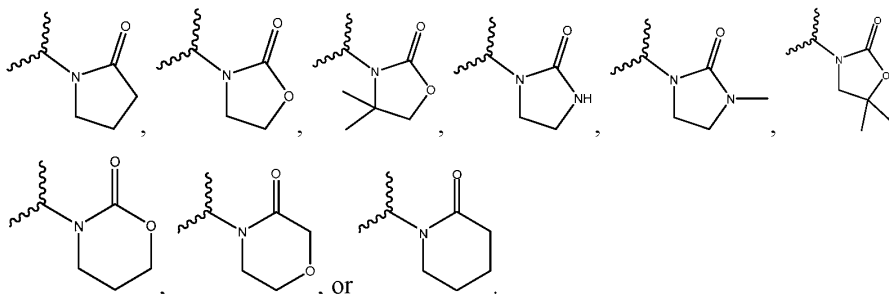
[0239] In yet another aspect of the invention, compounds of formula (I) and formula (II) are provided wherein Y is -C(O)-, s is 0, m is 0, R² is C₁-C₄ alkyl or aralkyl, and R⁶ is heterocyclyl, wherein the heterocyclyl is piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl. In certain embodiments of this aspect, Y is -C(O)-, s is 0, m is 0, R² is methyl, and R⁶ is piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl or thiomorpholinyl. In certain other embodiments of this aspect, Y is -C(O)-, s is 0, m is 0, R² is benzyl, and R⁶ is piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl or thiomorpholinyl.

[0240] In yet another aspect of the invention, compounds of formula (I) and formula (II) are provided wherein Y is -C(O)-, L is ethylene, and R⁶ is heterocyclyl optionally independently substituted one or more C₁-C₃ alkyl. In certain embodiments, the heterocyclyl optionally independently substituted one or more C₁-C₃ alkyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, tetrahydropyranyl, 1,3-dioxolanyl, 1,4-dioxanyl, morpholinyl, dimethyl-morpholinyl, thiomorpholinyl, 1,4-dithianyl, or 1,3,5-trithianyl. In other embodiments, the heterocyclyl is:





[0241] In yet another aspect of the invention, compounds of formula (I) and formula (II) are provided wherein Y is -C(O)-, L is propylene, and R⁶ is heterocyclyl optionally independently substituted one or more C₁-C₃ alkyl. In certain embodiments, the heterocyclyl optionally independently substituted one or more C₁-C₃ alkyl is azetidiny, pyrrolidiny, pyrazolidiny, piperidiny, piperaziny, 4-methyl-piperaziny, 4-acyl-piperaziny, tetrahydropyrany, 1,3-dioxolany, 1,4-dioxany, morpholiny, dimethyl-morpholiny, thiomorpholiny, 1,4-dithiany, or 1,3,5-trithiany. In other embodiments, the heterocyclyl is:



In other embodiments of this aspect, R⁶ is -NR⁴R⁷. In certain embodiments, R⁷ is hydroxyl, alkoxy, -SO₂C₁-C₆alkyl, -SO₂cycloalkyl, or -SO₂aryl, wherein the cycloalkyl or aryl of each of the -SO₂cycloalkyl and -SO₂aryl is optionally independently substituted with one or more R⁸.

[0242] In certain embodiments, compounds of formula (I) and formula (II) wherein Y is -C(O)- are:

[0243] 1-morpholino-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;

[0244] N-methoxy-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide;

[0245] 1-morpholino-3-phenyl-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;

[0246] 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanoic acid;

[0247] 1-morpholino-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;

[0248] N-(methylsulfonyl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide;

- [0249] 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-(piperazin-1-yl)propan-1-one;
- [0250] 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-N-(phenylsulfonyl)propanamide;
- [0251] 1-(4-methylpiperazin-1-yl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;
- [0252] N-(ethylsulfonyl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide;
- [0253] 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-thiomorpholinopropan-1-one;
- [0254] 1-(4-methylpiperazin-1-yl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butan-1-one;
- [0255] 4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-(piperazin-1-yl)butan-1-one;
- [0256] 1-morpholino-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butan-1-one;
- [0257] 4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-N-(phenylsulfonyl)butanamide;
- [0258] 4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanoic acid;
- [0259] N-(cyclopropylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide;
- [0260] N-(ethylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide;
- [0261] N-(methylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide;
- [0262] 1-(*cis*-2,6-dimethylmorpholino)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;
- [0263] and pharmaceutically acceptable salts of the foregoing compounds, including, but not limited to, dihydrochloride salts.
- [0264] In still yet another aspect of the invention, Y is -NR⁴SO₂- and R⁶ is C₁-C₆ alkyl, cycloalkyl or aryl, wherein the cycloalkyl or the aryl is optionally independently substituted with one or more C₁-C₃ alkyl, halogen, haloalkyl, amino or cyano.
- [0265] In certain embodiments, compounds of formula (I) and formula (II) wherein Y is -NR⁴SO₂- are:

- [0266] N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)methanesulfonamide;
- [0267] N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)benzenesulfonamide;
- [0268] N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)propane-2-sulfonamide;
- [0269] N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propyl)methanesulfonamide;
- [0270] N-methyl-N-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)methanesulfonamide;
- [0271] N-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)methanesulfonamide;
- [0272] N-methyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)methanesulfonamide; and
- [0273] N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)cyclopropanesulfonamide;
- [0274] and pharmaceutically acceptable salts of the foregoing compounds, including, but not limited to, dihydrochloride salts.
- [0275] In another aspect of the invention, Y is $-\text{SO}_2\text{NR}^4-$ and R^6 is $\text{C}_1\text{-C}_6$ alkyl or aryl, wherein the aryl is optionally independently substituted with one or more $\text{C}_1\text{-C}_3$ alkyl, halogen, haloalkyl, amino or cyano.
- [0276] In certain embodiments of this aspect of the invention, compounds of formula (I) and formula (II) wherein Y is $-\text{SO}_2\text{NR}^4-$ are
- [0277] N-phenyl-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethane-1-sulfonamide;
- [0278] N-methyl-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethane-1-sulfonamide;
- [0279] and pharmaceutically acceptable salts of the foregoing compounds, including, but not limited to, dihydrochloride salts.
- [0280] In still yet another aspect of the invention, Y is $-\text{NR}^4\text{C}(\text{O})\text{NR}^4\text{R}^4$ and each R^4 is $\text{C}_1\text{-C}_3$ alkyl. An exemplary compound wherein Y is $-\text{NR}^4\text{C}(\text{O})\text{NR}^4\text{R}^4$ is 1,1-dimethyl-3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)urea.
- [0281] The compounds of formula (I) and formula (II) may be formulated into pharmaceutical compositions.

PHARMACEUTICAL COMPOSITIONS

[0282] In another aspect, the invention provides pharmaceutical compositions comprising a LSD1 inhibitor according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other embodiments, administration may preferably be by the oral route.

[0283] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, *e.g.*, Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[0284] As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[0285] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg

per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0286] The pharmaceutical compositions comprising compounds of the present invention may be used in the methods described herein.

METHODS OF USE

[0287] In yet another aspect, the invention provides for methods for inhibiting LSD1 activity in a cell, comprising contacting the cell in which inhibition of LSD1 activity is desired with a therapeutically effective amount of a compound of formula (I), pharmaceutically acceptable salts thereof or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt thereof.

[0288] The compositions and methods provided herein are particularly deemed useful for inhibiting LSD1 activity in a cell. In one embodiment, a cell in which inhibition of LSD1 activity is desired is contacted with a therapeutically effective amount of a compound of formula (I) to negatively modulate the activity of LSD1. In other embodiments, a therapeutically effective amount of pharmaceutically acceptable salt or pharmaceutical compositions containing the compound of formula (I) may be used.

[0289] By negatively modulating the activity of LSD1, particularly in cases for cells overexpressing the LSD1 enzyme or somatic mutations that activate the LSD1 enzyme, the methods are designed to restore normal cellular transcription expression patterns, *e.g.*, by altering methylation pattern of H3K4, to inhibition undesired cellular proliferation resulting from enhanced LSD1 activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative modulation of LSD1. The degree of mono- and dimethylation of histone H3K4 may be monitored in the cell using well known methods, including those described in Example 83 below, to assess the effectiveness of treatment and dosages may be adjusted accordingly by the attending medical practitioner.

[0290] In another aspect, methods of treating cancer comprising administering to a patient having cancer a therapeutically effective amount of a compound of formula (I), pharmaceutically

acceptable salts thereof or pharmaceutical compositions comprising the compound or pharmaceutically acceptable salts thereof are provided.

[0291] The compositions and methods provided herein may be used for the treatment of a wide variety of cancer including tumors such as prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma,

pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is non-small cell lung cancer.

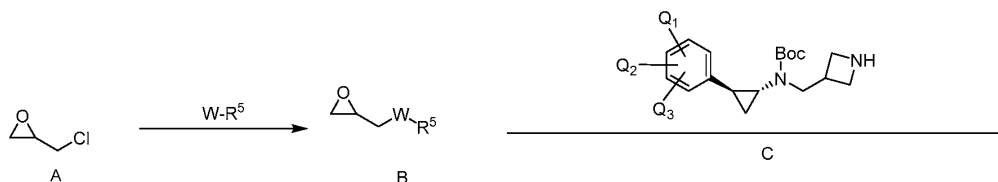
[0292] The concentration and route of administration to the patient will vary depending on the cancer to be treated. The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, *e.g.*, chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively. The degree of mono- and dimethylation of histone H3K4 may be monitored in the patient using well known methods, including those described in Example 83 below, to assess the effectiveness of treatment, along with other prognostic or biological factors, and dosages may be adjusted accordingly by the attending medical practitioner.

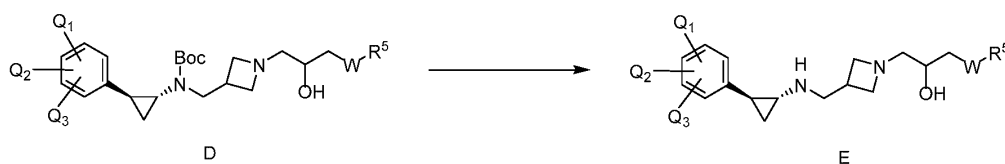
REACTION SCHEMES AND EXAMPLES

[0293] The compounds of the present invention may be prepared using commercially available reagents using the synthetic methods and reaction schemes described herein, or using other reagents and conventional methods well known to those skilled in the art.

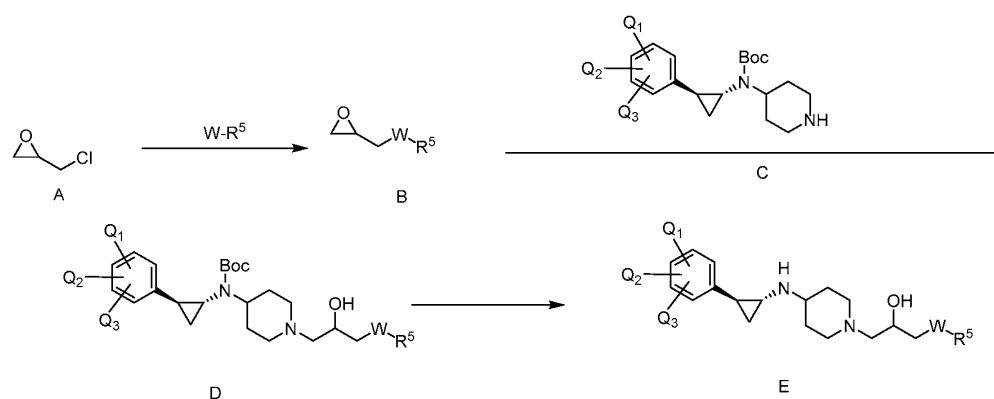
[0294] For instance, compounds of the present invention may be prepared according to the general reaction schemes I - V.

Scheme Ia



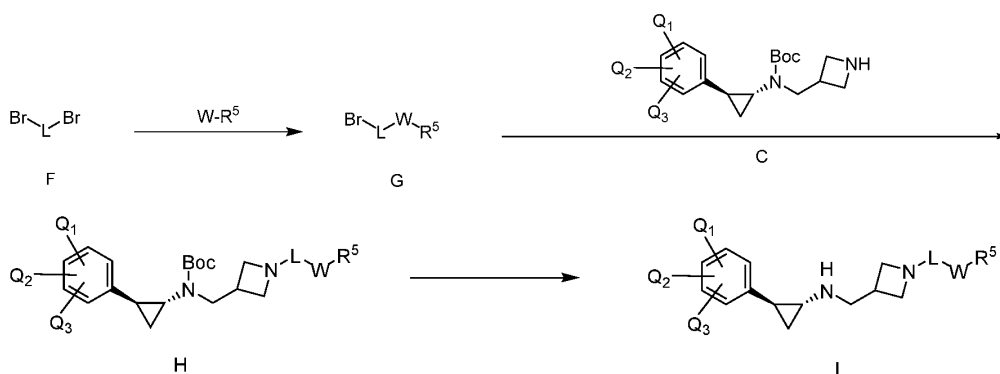


Scheme Ib

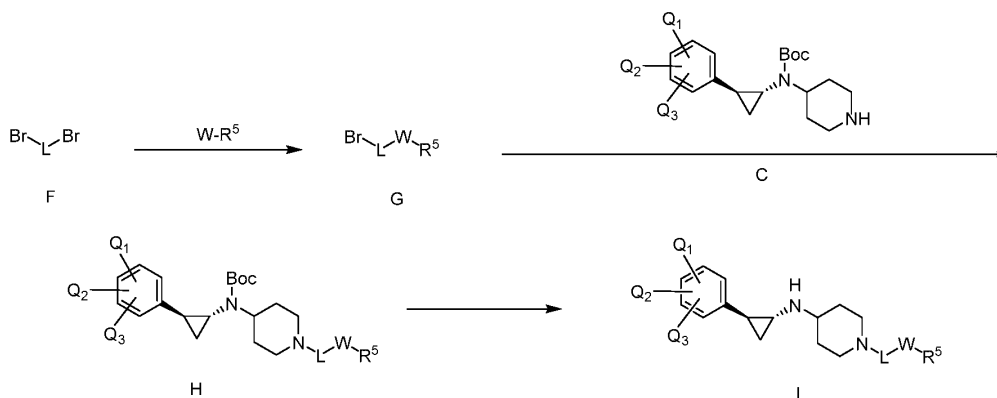


[0295] Schemes Ia and Ib illustrate preparation of compounds of formula (I) or formula (II), respectively, wherein W is NR^4 or O, (or Y is S, SO, or SO_2) and L is an epichlorohydrin derivative. The epichlorohydrin A undergoes substitution with nucleophile W-R^5 to afford intermediate B (Step 1). The substitution proceeds in solvents such as MeCN in the presence of a base such as K_2CO_3 , typically at an elevated temperature. In the case where Y is SO or SO_2 , the initial substitution with a nucleophile of the form R^6SH will be followed by oxidation to the sulfoxide or sulfone derivative yielding Y-R^6 . Reaction of B with amines C affords compounds D (Step 2). The epoxide ring opening also typically proceeds under conditions similar to Step 1. Removal of the protecting group in Step 3 to afford compounds E typically proceeds with an acid such as TFA in a solvent such as DCM.

Scheme IIa

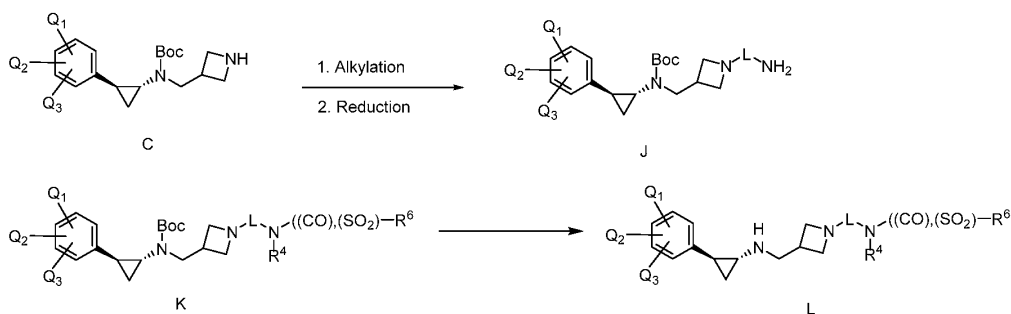


Scheme IIb

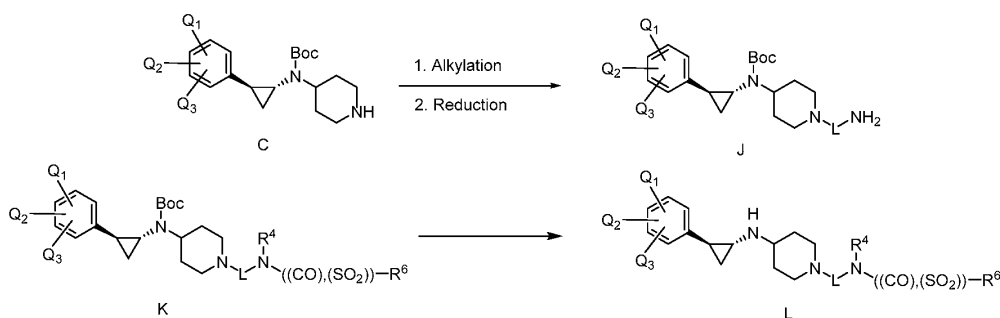


[0296] Schemes IIa and IIb illustrate preparation of compounds of formula (I) and formula (II), respectively, wherein W is NR^4 or O, (or Y is S, SO or SO_2), and L is an alkyl derivative. Reagent F undergoes substitution with nucleophile W-R^5 to afford intermediate G (Step 1). The substitution proceeds in solvents such as acetone in the presence of a base such as K_2CO_3 . In the case where Y is SO or SO_2 , the initial substitution with a nucleophile of the form R^6SH will be followed by oxidation to the sulfoxide or sulfone derivative yielding Y-R^6 . Reaction of G with amines C affords compounds H (Step 2). This substitution typically proceeds under conditions similar to Step 1. Alternative bases and solvents such as Cs_2CO_3 and MeCN may also be effective. Removal of the protecting group in Step 3 to afford compounds I typically proceeds with an acid such as TFA in a solvent such as DCM.

Scheme IIIa

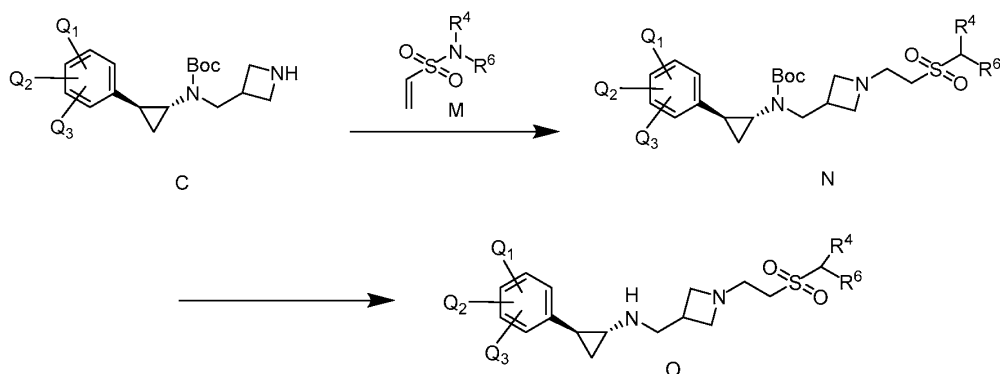


Scheme IIIb

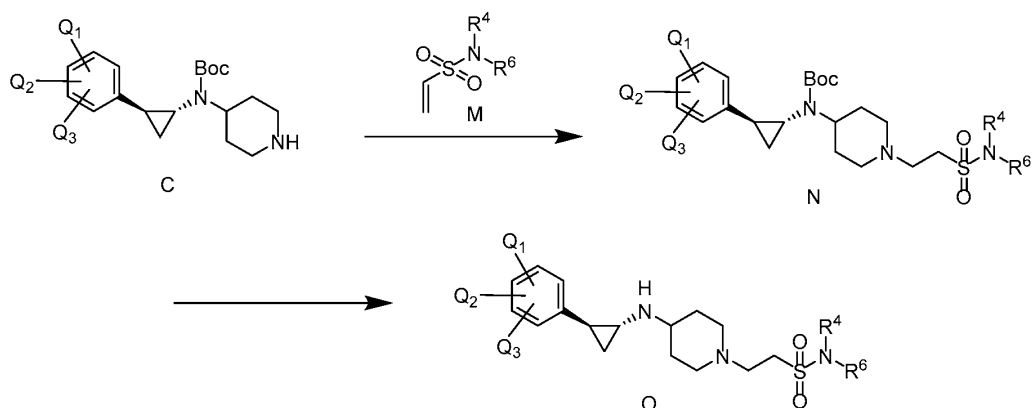


[0297] Scheme IIIa and Scheme IIIb illustrate preparation of compounds of formula (I) and formula (II), respectively, wherein Y is NR^4SO_2 or $\text{NR}^4\text{C}(\text{O})$. Intermediate C undergoes alkylation with a nitrile derivative, which is subsequently reduced to afford free amines J. In one case, alkylation with, for example, chloromethyl acetonitrile in a solvent such as acetone with a base such as K_2CO_3 would afford an intermediate that could be reduced to give the amine where L is $-\text{CH}_2\text{CH}_2-$. Alternatively, amines J could arise from the alkylation of intermediates C with a protected amine derivative. Functionalization of amines J would give rise to derivatives K, which would give targets L upon deprotection. The functionalization of K would proceed, for example, by reaction with sulfonyl or acyl chlorides. Removal of the Boc protecting group in the final step proceeds with acids such as TFA in solvents such as DCM.

Scheme IVa

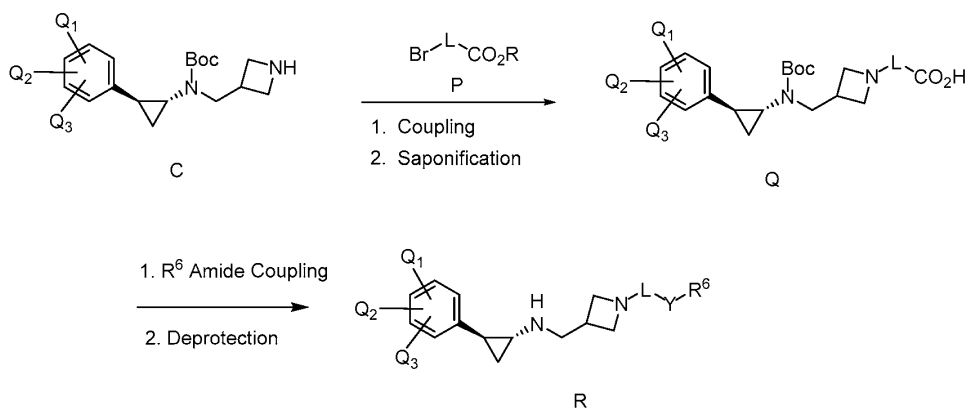


Scheme IVb

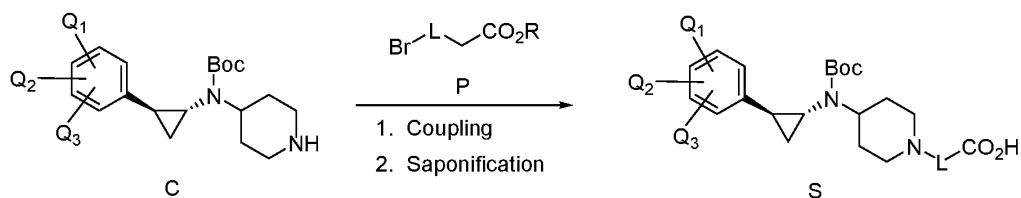


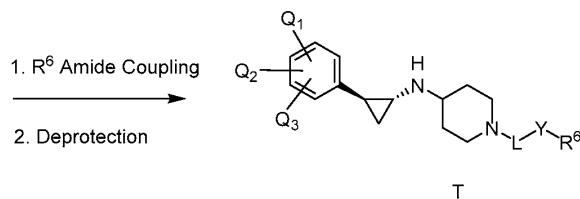
[0298] Schemes IVa and IVb illustrate preparation of compounds of formula (I) and formula (II), respectively, wherein Y is SO_2NR^4 . Intermediate C undergoes addition, for example with a vinyl sulfonamide derivative M, to afford compounds N. Removal of the Boc protecting group in the final step proceeds with acids such as TFA in solvents such as DCM to afford derivatives O.

Scheme Va



Scheme Vb

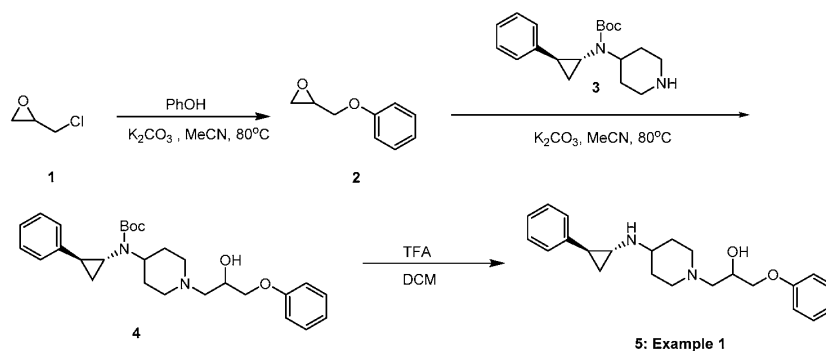




[0299] Schemes Va and Vb illustrate preparation of compounds of formula (I) and formula (II), respectively, wherein Y is -CO-. Intermediate C is alkylated with a halogen derivative P and the ester is cleaved to afford carboxylic acids S. This substitution proceeds in a solvent such as DMF with a base such as TEA and potassium iodide. Removal of the ester group occurs with a base such as NaOH in a solvent such as THF. Amide bond formation with a species R⁶ followed by removal of the protecting group affords compounds T. The amidation using R⁶ reaction proceeds, for example, in dichloromethane with EDC/HOBt. Removal of the Boc group proceeds, for example, with a dilute solution of HCl in dioxane.

[0300] The following Examples are intended to illustrate further certain embodiments of the invention and are not intended to limit the scope of the invention.

EXAMPLE 1



1-phenoxy-3-[4-[[trans-2-phenylcyclopropyl] amino]-1-piperidyl] propan-2-ol (5)

Step 1. 2-(phenoxymethyl)oxirane (2)

[0301] A solution of 2-(chloromethyl)oxirane (3.93 g, 42.5 mmol, 3.33 mL, 2.00 eq), phenol (2.00 g, 21.3 mmol, 1.87 mL, 1.00 eq) and K₂CO₃ (8.81 g, 63.8 mmol, 3.00 eq) in MeCN (40.0 mL) was stirred at 80 °C for 12 hours. After completion, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (eluent: PE/EA 25/1) to give 2-(phenoxymethyl)oxirane (2.20 g, 13.9 mmol, 65.5 % yield, 95.0 % purity) as a colorless oil. LCMS [M+41+1]: 192.

[0302] ¹H NMR (400MHz, methanol-d₄) δ = 7.27 - 7.23 (m, 2H), 6.94 - 6.91 (m, 3H), 4.28 - 4.25 (dd, J=11.2, 2.4 Hz, 1H), 3.86 - 3.81 (dd, J=11.2, 6.0 Hz, 1H), 3.32 - 3.30 (m, 1H), 2.86 - 2.83 (dd, J=5.2, 4.4 Hz, 1H), 2.72 - 2.71 (dd, J=5.2, 2.8 Hz, 1H).

Step 2. tert-butyl (1-(2-hydroxy-3-phenoxypropyl)piperidin-4-yl)-N-(trans-2-phenylcyclopropyl)carbamate (4)

[0303] A suspension of 2-(phenoxyethyl)oxirane (200 mg, 1.33 mmol, 1.00 eq), tert-butyl N-[trans-2-phenylcyclopropyl]-N-(4-piperidyl) carbamate (421 mg, 1.33 mmol, 1.00 eq) and K₂CO₃ (368 mg, 2.66 mmol, 2.00 eq) in MeCN (5.00 mL) was stirred at 80 °C for 14 hours. After completion, the mixture was filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (PE/EA 1/0 to 5/1) to give tert-Butyl N-[1-(2-hydroxy-3-phenoxy-propyl)-4-piperidyl]-N-[trans-2-phenylcyclo propyl]carbamate (400 mg, 857 umol, 64.5 % yield) as colorless oil. LCMS [M+1]: 467.

[0304] ¹H NMR (400MHz, chloroform-d) δ = 7.32 - 7.27 (m, 4H), 7.22 - 7.18 (m, 1H), 7.11 - 7.09 (m, 2H), 6.95 - 6.93 (m, 3H), 4.08 - 4.06 (m, 1H), 4.00 - 3.98 (m, 2H), 3.74 - 3.71 (m, 1H), 3.09 - 2.92 (m, 2H), 2.59 - 2.52 (m, 3H), 2.39 (m, 1H), 2.14 - 2.13 (m, 2H), 2.08 - 2.06 (m, 2H), 1.82 - 1.74 (m, 2H), 1.45 (m, 9H), 1.42 - 1.40 (m, 1H), 1.27 - 1.16(s, 1H)

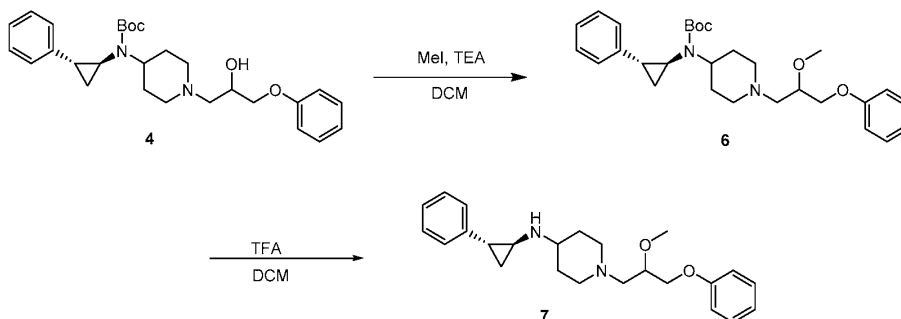
Step 3. 1-phenoxy-3-(4-(((trans)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol (5)

[0305] A solution of tert-butyl N-[1-(2-hydroxy-3-phenoxy-propyl)-4-piperidyl]-N-[trans-2-phenylcyclopropyl]carbamate (150 mg, 321 umol, 1.00 eq) and TFA (366 mg, 3.21 mmol, 238 uL, 10.0 eq) in DCM (5.00 mL) was stirred at 28 °C for 1 hour. After completion, saturated NaHCO₃ (10 mL) was added into the mixture. The mixture was extracted with DCM (3 × 20mL), the combined organic phase was concentrated under vacuum. The residue was purified by Prep-HPLC (Instrument: GX-A; Column: PhenomenexGemini 150*25mm*10um; Condition: water (0.05% ammonia hydroxide v/v)-ACN; Begin B: 55; End B: 85; Gradient Time (min): 12; 100%B Hold Time (min): 2; FlowRate(ml/min): 25). 1-phenoxy-3-(4-(((trans)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol (5) (51.0 mg, 139 umol, 43.3 % yield) was obtained as yellow oil. LCMS [M+1]: 367

[0306] ¹H NMR (400MHz, methanol-d₄) δ = 7.27 - 7.21 (m, 4H), 7.14 - 7.12 (m, 1H), 7.05 - 7.03 (m, 2H), 6.94 - 6.92 (m, 3H), 4.13 (m, 1H), 4.12 - 3.91 (m, 2H), 3.07 (m, 2H), 2.65 - 2.60 (m, 3H), 2.33 - 2.31 (m, 3H), 1.95 - 1.90 (m, 3H), 1.55 - 1.52 (m, 2H), 1.09 - 1.03 (m, 2H).

EXAMPLE 2

1-(2-methoxy-3-phenoxy-propyl)-N-[trans-2-phenylcyclopropyl]piperidin-4-amine (7)



Step 1. *tert*-butyl *N*-[1-(2-methoxy-3-phenoxy-propyl)-4-piperidyl]-*N*-[*trans*-2-phenylcyclopropyl]carbamate (6)

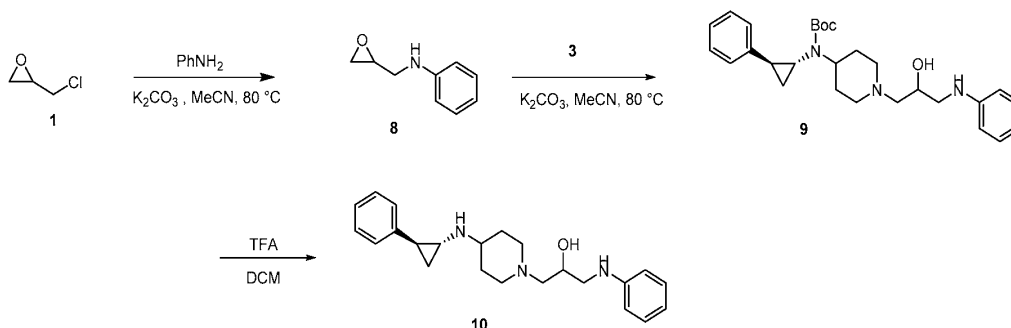
[0307] To a solution of **4** (150 mg, 321 μ mol, 1.00 eq) in THF (5.00 mL) was added NaH (15.4 mg, 6.4 mmol, 2.00 eq) at 0 °C. After stirring for 1 hour, MeI (2.41 g, 17.0 mmol, 1.06 mL, 52.8 eq) was added at 0 °C. The mixture was stirred at 28 °C for 2 hours. After completion, the mixture was poured into saturated NH₄Cl aq (20 mL), extracted with DCM (3 $\times$ 30 mL), and the combined organic phase was concentrated under vacuum. The residue was purified by Prep-TLC (PE/EA 2/1, R_f=0.8). *tert*-butyl *N*-[1-(2-methoxy-3-phenoxy-propyl)-4-piperidyl]-*N*-[*trans*-2-phenylcyclopropyl]carbamate (90.0 mg, 180 μ mol, 56.1 % yield, 96.2 % purity) was obtained as a yellow oil. LCMS [M+1]: 481

[0308] ¹H NMR (400MHz, methanol-d₄) δ = 7.27 – 7.22 (m, 4H), 7.12 – 7.10 (m, 3H), 6.95 – 6.92 (m, 3H), 4.09 – 4.08 (m, 1H), 4.03 – 3.99 (m, 1H), 3.75 – 3.70 (m, 2H), 3.48 (s, 3H), 3.20 – 3.02 (m, 2H), 2.68 – 2.60 (m, 3H), 2.28 – 2.08 (m, 5H), 1.75 (m, 2H), 1.42 – 1.39 (m, 10H), 1.29 – 1.24 (m, 1H).

Step 2. 1-(2-methoxy-3-phenoxy-propyl)-N-[trans-2-phenylcyclopropyl] piperidin-4-amine (7)

[0309] Treatment of compound **6** with TFA in a manner similar to Example 1 afforded the title compound as a yellow oil (66.0 mg, 160 μ mol, 85.2 % yield, 92 % purity). LCMS [M+1]: 381

[0310] ¹H NMR (400MHz, methanol-d₄) δ = 7.28 – 7.22 (m, 4H), 7.15 – 7.09 (m, 1H), 7.05 – 7.03 (m, 2H), 6.94 – 6.91 (m, 3H), 4.11 – 4.07 (m, 1H), 4.02 – 3.98 (m, 1H), 3.77 (m, 1H), 3.48 – 3.47 (m, 3H), 3.05 (m, 2H), 2.68 – 2.66 (m, 3H), 2.35 – 2.27 (m, 3H), 1.95 – 1.91 (m, 3H), 1.63 – 1.44 (m, 2H), 1.09 – 1.03 (m, 2H).

EXAMPLE 3**1-anilino-3-[4-[[trans-2-phenylcyclopropyl]amino]-1-piperidyl] propan-2-ol (10)**

[0311] Following the general procedure of Example 1, compound **10** was prepared from compound **1**:

Step 1. N-(oxiran-2-ylmethyl)aniline (**8**)

[0312] After completion, the mixture was filtered and the filtrate was concentrated. The residue was purified by Prep-HPLC (Instrument: HPLC-D; Column: Phenomenex Synergi Max-RP 250*80 10u; Condition: water (0.1%TFA)-ACN; Begin B: 0; End B: 25%ACN; Gradient Time (min): 37MIN; 52%; FlowRate(ml/min): 80). Compound **8** (800 mg, 3.22 mmol, 15.0 % yield, 60.0 % purity) was obtained as colorless oil. LCMS [M+1]: 150.

[0313] ¹H NMR (400MHz, methanol-d₄) δ = 7.36 - 7.07 (m, 1H), 6.65 - 6.60 (m, 1H), 3.42 - 3.39 (m, 1H), 3.16 - 3.13 (m, 2H), 2.77 - 2.75 (m, 1H), 2.63 - 2.61 (m, 1H)

Step 2. tert-butyl N-[1-(3-anilino-2-hydroxy-propyl)-4-piperidyl]-N-[trans-2-phenylcyclopropyl]carbamate (**9**)

[0314] After completion, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (eluent: PE/EA 1/0 to 5/1). Compound **9** (250 mg, 537 umol, 53.2 % yield) was obtained as colorless oil. LCMS [M+1]: 466.

[0315] ¹H NMR (400MHz, methanol-d₄) δ = 7.29 - 7.20 (m, 2H), 7.22 - 7.09 (m, 5H), 6.66 - 6.61 (m, 3H), 4.15 - 4.13 (m, 1H), 3.96 - 3.71 (m, 2H), 3.18 - 3.06 (m, 4H), 2.63 - 2.60 (m, 3H), 2.39 - 2.18 (m, 2H), 2.13 - 2.09 (m, 2H), 1.76 (m, 2H), 1.42 - 1.37 (m, 10H), 1.26 - 1.23 (m, 1H).

Step 3. 1-anilino-3-[4-[[trans-2-phenylcyclopropyl] amino]-1-piperidyl] propan-2-ol (**10**)

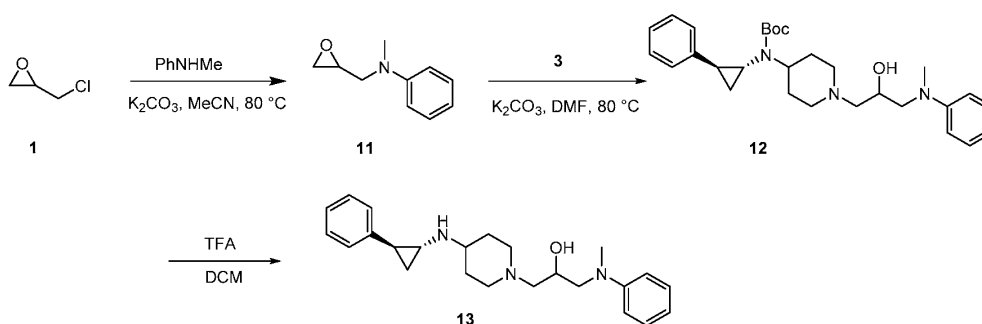
[0316] After completion, saturated NaHCO₃ (10 mL) was added into the mixture. The mixture was extracted with DCM (3 × 20mL), the combined organic phase was concentrated under vacuum. The residue was purified by Prep-HPLC (Instrument: GX-I; Column: YMC-

ActusODS-AQ 150*30 5u; Condition: water (0.1%TFA)-ACN; Begin B: 8; End B: 38; Gradient Time (min): 11; 100%B Hold Time (min): 2; FlowRate (ml/min): 25). Compound **10** (83.0 mg, 189 umol, 35.3 % yield, 2HCl) was obtained as yellow oil. LCMS [M+1]: 366.

[0317] ^1H NMR (400MHz, methanol- d_4) δ = 7.31 (m, 2H), 7.25 – 7.23 (m, 1H), 7.18 – 7.14 (m, 4H), 6.76 – 6.71 (m, 3H), 4.25 – 4.23 (dd, J =10.4, 3.2 Hz, 1H), 3.81 – 3.77 (m, 2H), 3.67 (m, 1H), 3.35 (m, 1H), 3.25 – 3.19 (m, 5H), 3.00 – 2.99 (m, 1H), 2.49 – 2.39 (m, 3H), 2.11 (m, 2H), 1.55 – 1.51 (m, 1H), 1.47 – 1.43 (m, 1H)

EXAMPLE 4

1-(N-methylanilino)-3-[4-[[trans-2-phenylcyclopropyl]amino]-1-piperidyl]propan-2-ol



[0318] Following the general procedure of Example 1, compound **13** was prepared from compound **1**:

Step 1. N-methyl-N-(oxiran-2-ylmethyl)aniline (**11**).

[0319] After completion, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC (Instrument: SFC-A; Column: Daiso 250*50mm, 10um; Condition: water (0.1%TFA)-ACN; Begin B: 0%ACN; End B: 20%ACN; Gradient Time (min): 34MIN; 40%; FlowRate (ml/min): 80). Compound **11** (300 mg, 1.58 mmol, 8.47 % yield, 86.0 % purity) was obtained as a colorless oil.

[0320] ^1H NMR (400MHz, methanol- d_4) δ = 7.22 – 7.17 (m, 2H), 6.81 – 6.79 (d, J =8.0 Hz, 2H), 6.70 – 6.67 (m, 1H), 3.70 – 3.66 (m, 1H), 3.36 – 3.31 (m, 2H), 2.97 (s, 3H), 2.77 – 2.75 (m, 1H), 2.56 – 2.54 (m, 1H).

Step 2. tert-butyl N-[1-[2-hydroxy-3-(N-methylanilino)propyl]-4-piperidyl]-N-[trans-2-phenylcyclopropyl]carbamate (**12**)

[0321] After completion, the mixture was cooled to 28 °C, the precipitate was filtered off. The filtrate was concentrated under vacuum. The residue was purified by Prep-TLC (PE/EA 2/1, P1: Rf=0.6) Compound **12** (200 mg, 414 umol, 45.0 % yield, 99.2 % purity) was obtained as yellow oil. LCMS [M+1]: 480.

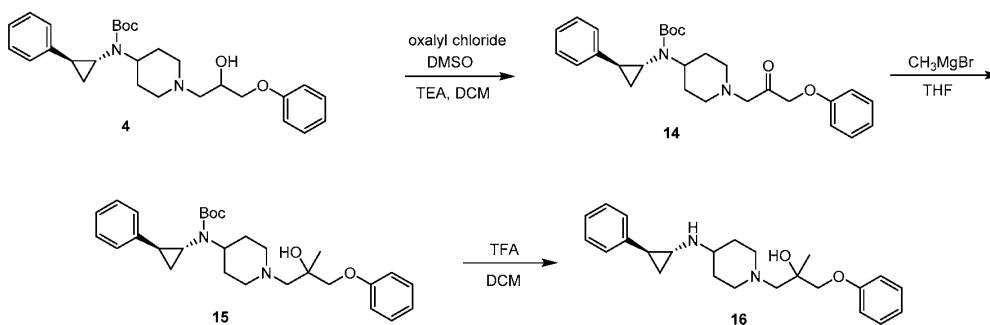
[0322] ^1H NMR (400MHz, methanol- d_4) δ = 7.26 - 7.22 (m, 2H), 7.16 - 7.10 (m, 5H), 6.78 - 6.76 (m, 2H), 6.65 (m, 1H), 4.13 (br. s., 1H), 3.76 - 3.75 (m, 1H), 3.39 - 3.31 (m, 4H), 2.99 (s., 3H), 2.67 - 2.64 (m, 5H), 2.13 - 2.11 (m, 3H), 1.90 - 1.83 (m, 2H), 1.42 - 1.37 (m, 10H), 1.24 - 1.22 (m, 1H)

[0323] After completion, the mixture was poured into saturated NaHCO_3 aq (20.0 mL), then extracted with DCM (2×30.0 mL). The combined organic phase was concentrated under vacuum. The residue was purified by Prep-TLC (eluent: DCM/MeOH 20/1). Compound **13** (60.0 mg, 148 μmol , 35.6 % yield, 93.8 % purity) was obtained as yellow oil. LCMS $[\text{M}+1]$: 380.

[0324] ^1H NMR (400MHz, methanol- d_4) δ = 7.22 - 7.20 (m, 2H), 7.16 - 7.12 (m, 3H), 7.05 - 7.03 (m, 2H), 6.77 - 6.75 (d, $J=8.8$ Hz, 2H), 6.64 - 6.63 (m, 1H), 4.08 - 4.05 (m, 1H), 3.44 (m, 1H), 3.27 (m, 1H), 3.15 - 3.02 (m, 2H), 2.98 (s, 3H), 2.78 - 2.67 (m, 1H), 2.57 - 2.53 (m, 2H), 2.33 - 2.31 (m, 3H), 2.98 - 1.90 (m, 3H), 1.54 (m, 2H), 1.09 - 1.03 (m, 2H).

EXAMPLE 5

2-methyl-1-phenoxy-3-(4-(((trans)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol (**16**)



Step 1. *tert*-butyl N-[1-(2-oxo-3-phenoxy-propyl)-4-piperidyl]-N-[(trans)-2-phenylcyclopropyl]carbamate (**14**).

[0325] To a solution of oxalyl chloride (212 mg, 1.67 mmol, 146 μL , 3.00 *eq*) in DCM (0.5 mL) was added DMSO (304 mg, 3.90 mmol, 304 μL , 7.00 *eq*) in DCM (0.5 mL), followed by *tert*-butyl N-[1-(2-hydroxy-3-phenoxy-propyl)-4-piperidyl]-N-[(trans)-2-phenylcyclopropyl]carbamate (260 mg, 557.21 μmol , 1.00 *eq*) in DCM (1 mL), then the mixture was stirred at -70°C for 1.5 hours. A solution of TEA (845 mg, 8.36 mmol, 1.16 mL, 15.00 *eq*) in DCM (0.5 mL) was added to the solution at -70°C , which was stirred at $-70 \sim -15^\circ\text{C}$ for 30 min. After completion, the mixture was quenched with water (10 mL), extracted with DCM (2×10 mL), the combined organic phase were washed with 1 N HCl (10 mL), saturated NaHCO_3

aqueous (10 mL), brine (10 mL), dried and concentrated to get the crude product. Compound *tert*-butyl N-[1-(2-oxo-3-phenoxy-propyl)-4-piperidyl]-N-[(trans)-2-phenylcyclopropyl]carbamate (240 mg, 479 μ mol, 86.12% yield, 92.9% purity) was obtained as a yellow solid. LCMS [M+1]: 465.4.

Step 2. *tert*-butyl N-[1-(2-hydroxy-2-methyl-3-phenoxy-propyl)-4-piperidyl]-N-[(1S,2R)-2-phenylcyclopropyl]carbamate (**15**).

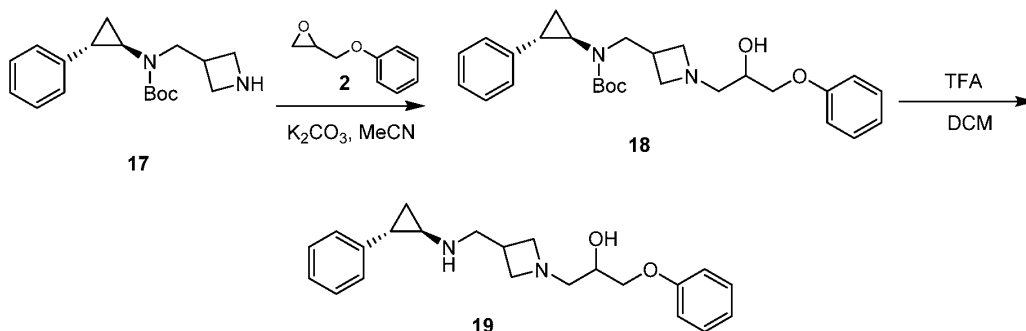
[0326] To a solution of *tert*-butyl N-[1-(2-oxo-3-phenoxy-propyl)-4-piperidyl]-N-[(trans)-2-phenylcyclopropyl]carbamate (240 mg, 516 μ mol, 1.00 eq) in THF (3.00 mL) was added CH_3MgBr (3 M, 344 μ L, 2.00 eq) dropwise at 0 °C, then the mixture was stirred at 0 ~ 20 °C for 3 hours. After completion, the mixture was quenched with water (5 mL), diluted with EA (20 mL), washed with saturated NaHCO_3 aq (10 mL), brine (10 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated under vacuum. Compound **15** (240 mg, 499 μ mol, 96% yield) was obtained as a yellow solid which was used for the next step directly without further purification. LCMS [M+1]: 481.2.

Step 3. 2-methyl-1-phenoxy-3-[4-[[1-(1S,2R)-2-phenylcyclopropyl]amino]-1-piperidyl]propan-2-ol (**16**).

[0327] To a mixture of *tert*-butyl N-[1-(2-hydroxy-2-methyl-3-phenoxy-propyl)-4-piperidyl]-N-[(trans)-2-phenylcyclopropyl]carbamate (240 mg, 499 μ mol, 1.00 eq) in DCM (4.00 mL) was added TFA (569 mg, 4.99 mmol, 369 μ L, 10.0 eq) in one portion at 20 °C, then the mixture was stirred at the same temperature for 1 hour. After completion, saturated NaHCO_3 aq (20 mL) was added into the mixture, the mixture was extracted with DCM (3 $\times$ 20 mL). The combined organic phase was washed with brine, dried and concentrated under vacuum. The residue was purified by prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5 μ ; Condition: water (0.225%FA)-ACN; Begin B: 6; End B: 36, Gradient Time (min): 11; 100%B Hold Time (min): 4; FlowRate (ml/min): 25) to give **16** as a colorless solid. LCMS [M+1]: 381.1.

[0328] ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.28 – 7.21 (m, 4H), 7.11 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 7.2 Hz, 2H), 6.93 - 6.90 (m, 3H), 3.86 - 3.84 (d, J = 7.2 Hz, 1H), 3.80 - 3.78 (d, J = 9.2 Hz, 1H), 2.95 - 2.88 (m, 2H), 2.58 - 2.54 (m, 1H), 2.49 (s, 2H), 2.29 – 2.22 (m, 3H), 1.89 - 1.79 (m, 3H), 1.46 - 1.40 (m, 2H), 1.25 (s, 3H), 1.07 - 0.97 (m, 3H)

EXAMPLE 6

1-phenoxy-3-[3-[[[(*trans*)-2-phenylcyclopropyl]amino]methyl]azetidin-1-yl]propan-2-ol (**19**)

Step 1. *tert*-butyl *N*-[[1-(2-hydroxy-3-phenoxy-propyl)azetidin-3-yl]methyl]-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate (**18**).

[0329] To a solution of *tert*-butyl *N*-(azetidin-3-ylmethyl)-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate (100 mg, 331 μ mol, 1.00 eq) in MeCN (3.00 mL) was added 2-(phenoxymethyl)oxirane **2** (74.5 mg, 496 μ mol, 67.1 μ L, 1.50 eq) and K_2CO_3 (45.7 mg, 331 μ mol, 1.00 eq). The mixture was stirred at 80 °C for 12 hours. After completion, the mixture was filtered and the filtrate was concentrated under vacuum. Water (10 mL) and HCl (1M, 1 mL) was added into the mixture. The resulting mixture was extracted with DCM (3 $\times$ 20 mL), the combined organic phase was concentrated under vacuum to give compound **18** (200 mg, crude) was obtained as yellow oil. The crude was used to the next step directly. LCMS [M+1]: 453.

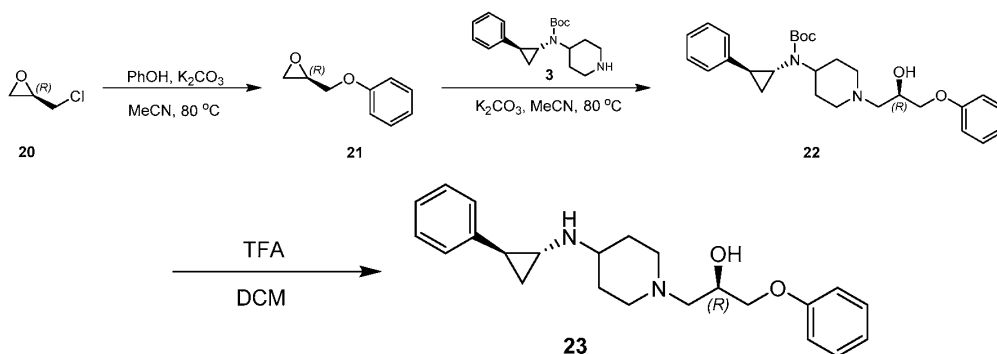
Step 2. 1-phenoxy-3-[3-[[[(*trans*)-2-phenylcyclopropyl]amino]methyl]azetidin-1-yl]propan-2-ol (**19**).

[0330] A solution of *tert*-butyl *N*-[[1-(2-hydroxy-3-phenoxy-propyl)azetidin-3-yl]methyl]-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate (200mg, 442 μ mol, 1.00 eq) and TFA (50.4 mg, 442 μ mol, 32.7 μ L, 1.00 eq) in DCM (3.00 mL) was stirred at 20 °C for 1 hour. After completion, saturated $NaHCO_3$ aq (10 mL) was added into the mixture, the mixture was extracted with DCM (3 $\times$ 20 mL). The combined organic phase was concentrated under vacuum. The residue was purified by Prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5 μ ; Condition: water (0.225%FA)-ACN; Begin B: 6; End B: 36, Gradient Time (min): 11; 100%B Hold Time (min): 4; FlowRate (ml/min): 25) to give 1-phenoxy-3-[3-[[[(*trans*)-2-phenylcyclopropyl]amino]methyl]azetidin-1-yl]propan-2-ol (25.0 mg, 71.0 μ mol, 16.1 % yield) as yellow solid. LCMS [M+1]: 353.

[0331] ^1H NMR (400 MHz, methanol- d_4) δ = 8.33 (br. s, 1H), 7.30 - 7.22 (m, 4H), 7.13 (m, 1H), 7.08 - 7.06 (m, 2H), 6.95 - 6.93 (m, 3H), 4.24 (br. s., 2H), 4.14 (br. s., 1H), 4.01 - 3.95 (m, 4H), 3.52 - 3.32 (m, 2H), 3.13 - 3.07 (m, 3H), 2.42 (br. s., 1H), 1.99 (br. s., 1H), 1.15 - 1.07 (m, 2H)

EXAMPLE 7

(*R*)-1-phenoxy-3-(4-(((1*S*,2*R*)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol (**23**)



Step 1. (*R*)-2-(phenoxy-methyl)oxirane (**21**).

[0332] To a solution of phenol (1.00 g, 10.6 mmol, 935 μL , 1.00 *eq*) in CH_3CN (20.0 mL) was added K_2CO_3 (4.41 g, 31.9 mmol, 3.00 *eq*) in one portion at 20 °C, followed by (*R*)-2-(chloromethyl)oxirane (1.97 g, 21.26 mmol, 1.67 mL, 2.00 *eq*), then the mixture was heated to 70~80 °C and stirred for 8 hours. After completion, the mixture was filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified over column chromatograph (PE/EA=50:1~20:1). Compound (*R*)-2-(phenoxy-methyl)oxirane (1.12 g, 7.35 mmol, 69% yield, 98.5% purity) was obtained as colorless oil.

Step 2. *N*-[1-[(*R*)-2-hydroxy-3-phenoxy-propyl]-4-piperidyl]-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate (**22**).

[0333] To a solution of (*R*)-2-(phenoxy-methyl)oxirane (100 mg, 666 μmol , 1.00 *eq*) and *tert*-butyl *N*-[(*trans*)-2-phenylcyclopropyl]-*N*-(4-piperidyl)carbamate (211 mg, 666 μmol , 1.00 *eq*) in CH_3CN (5.0 mL) was added K_2CO_3 (184 mg, 1.33 mmol, 2.00 *eq*) in one portion at 20 °C, then the mixture was heated to 80 °C and stirred for 18 hours. After completion, the mixture was filtered, and the filtration was concentrated to give the crude product which was purified over column chromatography (PE/EA=5:1~2:1). Compound **22** (200 mg, 407 μmol , 61% yield) was obtained as colorless oil. LCMS $[\text{M}+1]$: 467.2.

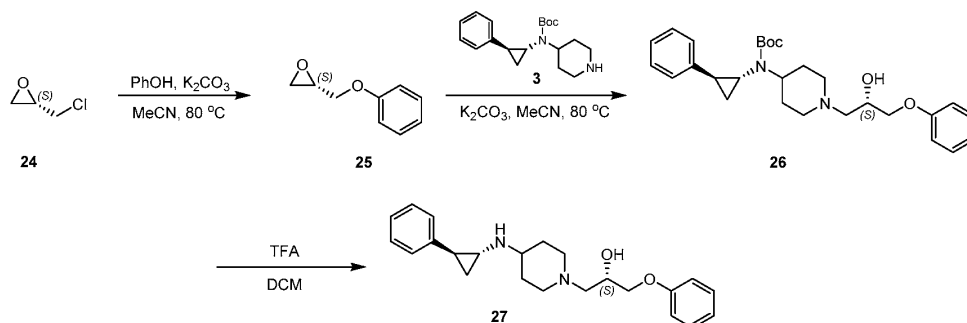
Step 3. (2R)-1-phenoxy-3-[4-[[[(trans)-2-phenylcyclopropyl] amino]-1-piperidyl]propan-2-ol (23).

[0334] To a mixture of **22** (200 mg, 428 μ mol, 1.00 eq) in DCM (4.00 mL) was added TFA (831 mg, 7.28 mmol, 540 μ L, 10.0 eq) in one portion at 20 °C, then the mixture was stirred at the same temperature for 1 hour. After completion, saturated NaHCO₃ aq (20 mL) was added into the mixture, the mixture was extracted with DCM (3 $\times$ 20 mL). The combined organic phase was washed with brine, dried and concentrated under vacuum. The residue was purified by prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5 μ ; Condition: water (0.225%FA)-ACN; Begin B: 6; End B: 36, Gradient Time (min): 11; 100%B Hold Time (min): 4; FlowRate (ml/min): 25) to give (2R)-1-phenoxy-3-[4-[[[(trans)-2-phenylcyclopropyl] amino]-1-piperidyl]propan-2-ol **23** (90.8 mg, 185 μ mol, 43.2 % yield, 98.0% purity) as a yellow solid. LCMS [M+1]: 367.1.

[0335] ¹H NMR (400 MHz, DMSO-d₆) δ = 7.30 – 7.22 (m, 4H), 7.20 - 7.11 (m, 1H), 7.03 – 7.01 (m, 2H), 6.94 – 6.92 (d, J =7.8 Hz, 3H), 4.78 - 4.77 (d, 1H), 3.97 - 3.94 (m, 1H), 3.93 - 3.87 (m, 1H), 3.85 - 3.81 (m, 1H), 2.90 - 2.72 (m, 2H), 2.45 - 2.36 (m, 1H), 2.34 (br. s., 2H), 2.24 - 2.16 (m, 1H), 2.08 - 1.94 (m, 2H), 1.82 - 1.67 (m, 3H), 1.41 - 1.19 (m, 2H), 0.96 - 0.92 (m, 2H).

EXAMPLE 8

(S)-1-phenoxy-3-(4-(((1S,2R)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol (27)



[0336] Following the general procedure of Example 7, compound **27** was prepared from compound **24**.

Step 1. (2S)-2-(phenoxy)methyloxirane (25).

[0337] After completion, the mixture was filtered and the filtrate was concentrated to give the crude product which was purified over column chromatograph (PE/EA=50:1~20:1). Compound **25** (1.12 g, 7.35 mmol, 69% yield, 98.5% purity) was obtained as colorless oil. LCMS [M+1]: 150.

Step 2. *tert*-butyl *N*-[1-[(2*S*)-2-hydroxy-3-phenoxy-propyl]-4- piperidyl]-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate (**26**).

[0338] Compound **26** (360 mg, 772 μ mol, 58% yield) was obtained as colorless oil. LCMS [M+1]: 467.

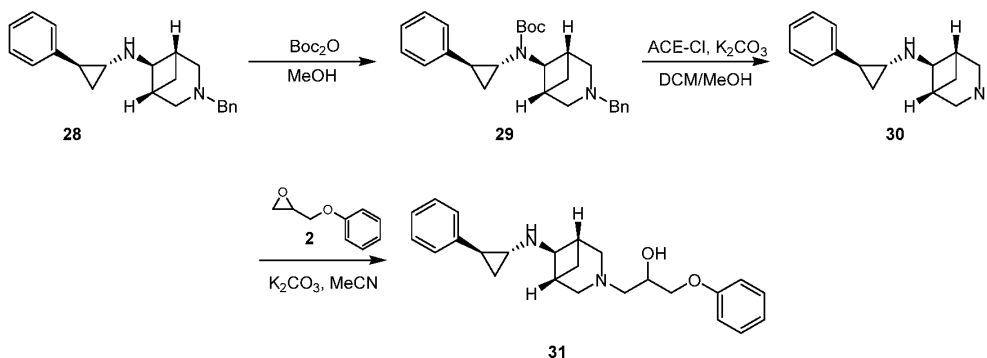
Step 3. (2*S*)-1-phenoxy-3-[4-[(*trans*)-2-phenylcyclopropyl]amino]-1-piperidyl]propan-2-ol (**27**)

[0339] The residue was purified by prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5 μ ; Condition: water (0.225%FA)-ACN; Begin B: 6; End B: 36, Gradient Time (min): 11; 100%B Hold Time (min): 4; FlowRate (ml/min): 25) to give (2*S*)-1-phenoxy-3-[4-[(*trans*)-2-phenylcyclopropyl]amino]-1-piperidyl]propan-2-ol (**27**) (179 mg, 371 μ mol, 51% yield, 99.7% purity) as a yellow solid. LCMS [M+1]: 367.

[0340] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.30 - 7.20 (m, 4H), 7.12 - 7.08 (m, 1H), 7.03 - 7.01 (m, 2H), 6.94 - 6.92 (d, *J* = 7.6 Hz, 3H), 4.79 - 4.78 (m, 1H), 3.99 - 3.93 (m, 1H), 3.93 - 3.87 (m, 1H), 3.86 - 3.80 (m, 1H), 2.90 - 2.72 (m, 2H), 2.45 - 2.36 (m, 1H), 2.34 (br. s., 2H), 2.24 - 2.16 (m, 1H), 2.08 - 1.94 (m, 2H), 1.82 - 1.67 (m, 3H), 1.33 - 1.25 (m, 2H), 0.95 - 0.93 (m, 2H)

EXAMPLE 9

1-phenoxy-3-[(1*R*,5*S*)-6-[(*trans*)-2-phenylcyclopropyl]amino]-3-azabicyclo[3.1.1]heptan-3-yl]propan-2-ol (**31**).



Step 1. *tert*-butyl *N*-[(5*S*)-3-benzyl-3-azabicyclo[3.1.1]heptan-6-yl]-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate (**29**).

[0341] To a solution of 3-benzyl-*N*-(2-phenylcyclopropyl)-3-azabicyclo[3.1.1]heptan-6-amine (50.0 mg, 157 μ mol, 1.00 *eq*) in MeOH (2.00 mL) was added (Boc)₂O (343 mg, 1.57 mmol, 361 μ L, 10.0 *eq*). The mixture was stirred at 50 °C for 15 hours. After completion, the mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE/EA from 100/1 to 5/1) to give *tert*-butyl *N*-[(5*S*)-3-benzyl-3-azabicyclo[3.1.1]heptan-6-yl]-

N-[(*trans*)-2-phenylcyclopropyl]carbamate **29** (50.0 mg, 119 μ mol, 76.1 % yield) as yellow oil. LCMS [M+1]: 419.

Step 2. (5*S*)-*N*-[(*trans*)-2-phenylcyclopropyl]-3-azabicyclo[3.1.1]heptan-6-amine (**30**).

[0342] To a solution of **29** (50.0 mg, 119 μ mol, 1.00 *eq*) and K₂CO₃ (144 mg, 1.43 mmol, 12.0 *eq*) in DCM (3.00 mL) was added 1-chloroethyl chloroformate (51.2 mg, 358 μ mol, 3.00 *eq*). After stirring at 20 °C for 1.5 hours, the reaction mixture was filtered. The filtrate was concentrated under vacuum. The residue was dissolved in MeOH (3.00 mL). The solution was refluxed (65 °C) for 2 hour. After completion, the mixture was filtered and concentrated under vacuum to give (5*S*)-*N*-[(*trans*)-2-phenylcyclopropyl]-3-azabicyclo[3.1.1]heptan-6-amine **30** (27.0 mg, crude) as yellow oil. The crude material was used to the next step directly.

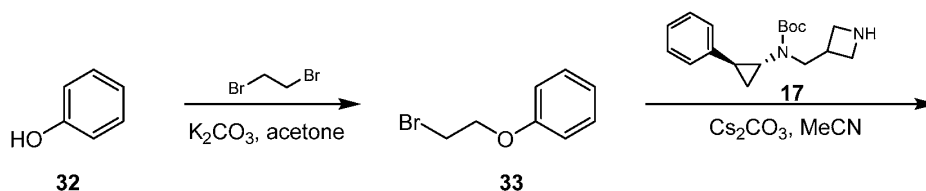
Step 3. 1-phenoxy-3-[(1*R*,5*S*)-6-[(*trans*)-2-phenylcyclopropyl]amino]-3-azabicyclo[3.1.1]heptan-3-yl]propan-2-ol (**31**).

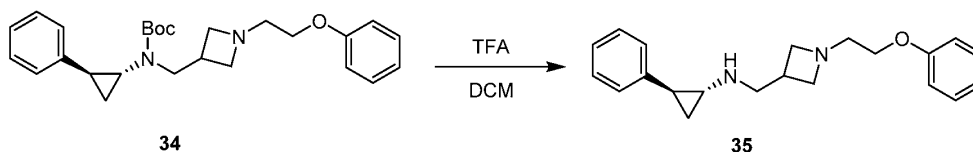
[0343] A mixture of **30** (27.0 mg, 118. μ mol, 1.00 *eq*), 2-(phenoxyethyl)oxirane (26.6 mg, 177 μ mol, 24.0 μ L, 1.50 *eq*) and K₂CO₃ (32.7 mg, 237 μ mol, 2.00 *eq*) in MeCN (5.00 mL) was stirred at 80 °C for 2 hours under N₂. After completion, the mixture was concentrated under vacuum and purified by Prep-HPLC (Instrument: GX-B; Column: Welch Ultimate AQ-C18 150*30mm*5 μ m; Condition: water(0.1%TFA)-ACN; Begin B: 22; End B: 52; Gradient Time(min): 12; 100%B Hold Time(min): 2; FlowRate(ml/min): 25) to give 1-phenoxy-3-[(1*R*,5*S*)-6-[(*trans*)-2-phenylcyclopropyl]amino]-3-azabicyclo[3.1.1]heptan-3-yl]propan-2-ol **31** (2.80 mg, 7.07 μ mol, 8.92 % yield, 95.6 % purity) as yellow oil. LCMS [M+1]: 379.

[0344] ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 7.32 - 7.26 (m, 4H), 7.24 - 7.22 (m, 1H), 7.18 - 7.16 (m, 2H), 6.96 - 6.94 (m, 3H), 4.41 (d, *J*=6.8 Hz, 1H), 4.06 - 4.00 (m, 4H), 3.76 (br. s., 3H), 3.53 - 3.48 (m, 2H), 3.01 (br. s., 1H), 2.85 (br. s., 3H), 2.50 (d, *J*=3.2 Hz, 1H), 2.15 - 2.12 (m, 1H), 1.56 - 1.51 (m, 1H), 1.42 - 1.36 (m, 1H).

EXAMPLE 10

(*trans*)-*N*-[[1-(2-phenoxyethyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine (**35**)





Step 1. 2-bromoethoxybenzene (33).

[0345] A mixture of phenol (200 mg, 2.13 mmol, 187 μ L, 1.00 *eq*), 1,2-dibromoethane (2.40 g, 12.8 mmol, 962 μ L, 6.00 *eq*) and K_2CO_3 (1.76 g, 12.8 mmol, 6.00 *eq*) in acetone (200 mL) was stirred at 80 °C under N_2 for 15 hours. After completion, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-TLC(PE/EA 10/1) to give 2-bromoethoxybenzene (160 mg, 738 μ mol, 35 % yield, 92.8 % purity) as colorless oil.

[0346] ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.29 - 7.25 (m, 2H), 6.94 - 6.91 (m, 3H), 4.30 - 4.27 (m, 2H), 3.69 - 3.63 (m, 2H).

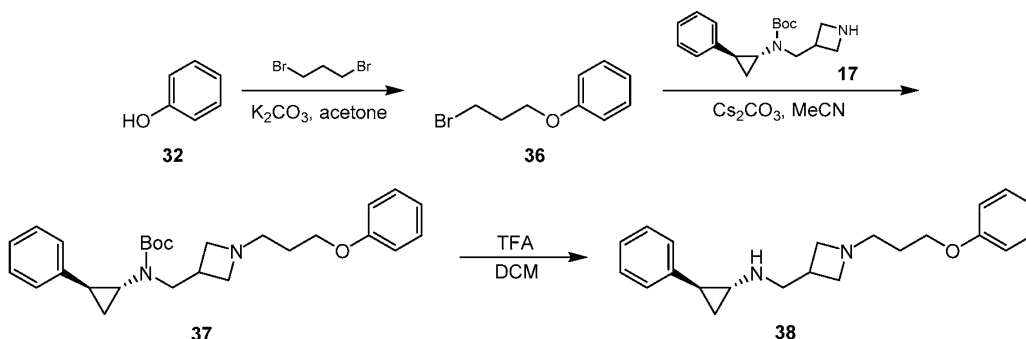
Step 2. tert-butyl N-[[1-(2-phenoxyethyl)azetidin-3-yl]methyl]-N-[(trans)-2-phenylcyclopropyl]carbamate (34).

[0347] A mixture of 33 (66.5 mg, 331 μ mol, 1.00 *eq*), 17 (100 mg, 331 μ mol, 1.00 *eq*) and Cs_2CO_3 (215 mg, 661 μ mol, 2.00 *eq*) in MeCN (2.00 mL) was stirred at 80 °C under N_2 for 2 hours. After completion, the mixture was filtered and the filtrate was concentrated under vacuum to give tert-butyl N-[[1-(2-phenoxyethyl)azetidin-3-yl]methyl]-N-[(trans)-2-phenylcyclopropyl]carbamate 34 (150 mg, crude) as yellow oil. LCMS [M+1]: 423.

Step 3. (trans)-N-[[1-(2-phenoxyethyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine (35).

[0348] A mixture of 34 (139 mg, 329 μ mol, 1.00 *eq*) and TFA (375 mg, 3.29 mmol, 244 μ L, 10.00 *eq*) in DCM (2.00 mL) was stirred at 10 °C for 1 hour. The mixture was concentrated under vacuum and purified by Prep-HPLC (Instrument: GX-E; Column: Phenomenex Synergi C18 150*30mm*4 μ m; Condition: water(0.05% HCl)-ACN; Begin B:16; End B: 36; Gradient Time(min):7.8; 100%B Hold Time(min): 2; FlowRate(ml/min): 25) to give (trans)-N-[[1-(2-phenoxyethyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine 35 (23.0 mg, 67.5 μ mol, 21 % yield, 94.6 % purity) as white solid. LCMS [M+1]: 323.

[0349] ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.35 – 7.29 (m, 4H), 7.24 – 7.18 (m, 3H), 7.01 – 6.97 (m, 3H), 4.43 (br. S., 2H), 4.33 – 4.25 (m, 4H), 3.70 – 3.57 (m, 4H), 3.44 – 3.40 (m, 1H), 3.01 – 3.00 (d, J =3.2 Hz, 1H), 2.61 – 2.58 (m, 1H), 1.63 – 1.59 (m, 1H), 1.43 – 1.29 (m, 1H).

EXAMPLE 11*(trans)*-*N*-[[1-(3-phenoxypropyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine (**38**)Step 1. 3-bromopropoxybenzene (**36**).

[0350] A mixture of phenol (200 mg, 2.13 mmol, 187 μ L, 1.00 *eq*), 1,3-dibromopropane (2.57 g, 12.8 mmol, 1.30 mL, 6.00 *eq*) and K_2CO_3 (1.76 g, 12.8 mmol, 6.00 *eq*) in acetone (200 mL) was stirred at 80 °C under N_2 for 15 hours. After completion, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-TLC (PE/EA 10/1) to give 3-bromopropoxybenzene (260 mg, 1.21 mmol, 57 % yield) as colorless oil.

[0351] 1H NMR (400 MHz, METHANOL- d_4) δ = 7.28 - 7.23 (m, 2H), 6.93 - 6.90 (m, 3H), 4.10 - 4.07 (t, J =3.6 Hz, 2H), 3.63 - 3.60 (t, J =6.4 Hz, 2H), 2.31 - 2.24 (m, 2H).

Step 2. *tert*-butyl *N*-[[1-(3-phenoxypropyl)azetidin-3-yl]methyl]-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate (**37**).

[0352] A mixture of **36** (71.1 mg, 331 μ mol, 1.00 *eq*), **17** (100 mg, 331 μ mol, 1.00 *eq*) and Cs_2CO_3 (215 mg, 661 μ mol, 2.00 *eq*) in MeCN (2.00 mL) was stirred at 80 °C under N_2 for 2 hours. After completion, the mixture was filtered and the filtrate was concentrated under vacuum to give *tert*-butyl *N*-[[1-(3-phenoxypropyl)azetidin-3-yl]methyl]-*N*-[(*trans*)-2-phenylcyclopropyl]carbamate **37** (200 mg, crude) as yellow oil. LCMS [$M+1$]: 437.

Step 3. (*trans*)-*N*-[[1-(3-phenoxypropyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine (**38**).

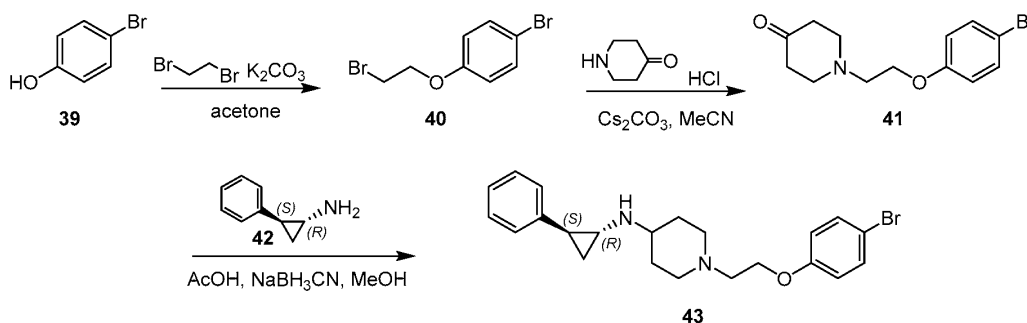
[0353] A mixture of **37** (144 mg, 330 μ mol, 1.00 *eq*) and TFA (376 mg, 3.30 mmol, 244 μ L, 10.0 *eq*) in DCM (2.00 mL) was stirred at 10 °C for 1 hour. After completion, the mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (Instrument: GX-E; Column: Phenomenex Synergi C18 150*30mm*4 μ m; Condition: water(0.05% HCl)-ACN; Begin B: 20; End B: 40; Gradient Time(min): 7.8; 100%B Hold Time(min): 2; FlowRate(ml/min): 28)

to give (*trans*)-*N*-[[1-(3-phenoxypropyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine **38** (10.0 mg, 29.0 μ mol, 9 % yield, 97.4 % purity) as colorless oil. LCMS [M+1]: 337.

[0354] ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.32 - 7.18 (m, 7H), 6.96 - 6.94 (m, 3H), 4.30 - 4.29 (m, 3H), 4.10 - 4.07 (m, 3H), 3.67 - 3.58 (m, 2H), 3.50 - 3.48 (m, 2H), 3.39 (m, 1H), 3.00 - 2.99 (m, 1H), 2.60 (br. s., 1H), 2.09 - 2.07 (d, J =6 Hz, 2H), 1.64 - 1.58 (m, 1H), 1.42 - 1.37 (m, 1H)

EXAMPLE 12

1-[2-(4-bromophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine



Step 1. 1-bromo-4-(2-bromoethoxy)benzene (**40**).

[0355] To a solution of 4-bromophenol (10.0 g, 57.8 mmol, 1.00 *eq*) and 1,2-dibromoethane (65.2 g, 347 mmol, 26.2 mL, 6.00 *eq*) in acetone (200mL) was added K_2CO_3 (47.9 g, 347 mmol, 6.00 *eq*). The mixture was stirred at 80 °C for 15 hours. After completion, the mixture was filtered and concentrated under vacuum. The residue was dissolved in water (50 mL) and extracted with DCM (2 $\times$ 100 mL). The combined organic phase was washed with brine (80 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum to give 1-bromo-4-(2-bromoethoxy)benzene (13.0 g, crude) as light brown solid. The crude was used to the next step directly.

Step 2. 1-[2-(4-bromophenoxy)ethyl]piperidin-4-one (**41**).

[0356] To a mixture of **40** (8.00 g, 28.6 mmol, 1.00 *eq*) and piperidin-4-one (7.75 g, 57.2 mmol, 2.00 *eq*, HCl) in MeCN (120 mL) was added Cs_2CO_3 (18.6 g, 57.2 mmol, 2.00 *eq*). The mixture was stirred at 80 °C for 15 hours under N_2 . After completion, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (PE/EA from 10/1 to 1/1) to give 1-[2-(4-bromophenoxy)ethyl]piperidin-4-one **41** (6.30 g, 16.5 mmol, 58 % yield, 78.0 % purity) as yellow oil. LCMS [M+1]: 299.

Step 3. 1-[2-(4-bromophenoxy)ethyl]-N-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (**43**).

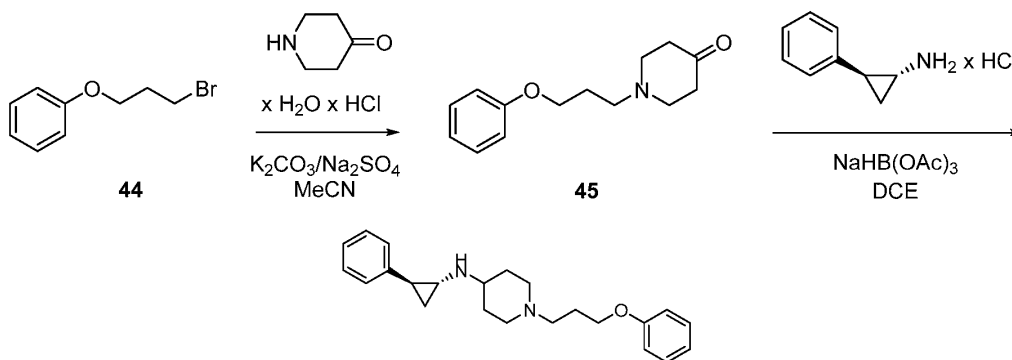
[0357] To a solution of **41** (269 mg, 901 μ mol, 1.20 *eq*) and (1*R*,2*S*)-2-phenylcyclopropanamine **42** (100 mg, 751 μ mol, 1.00 *eq*) in MeOH (3.00 mL) was added AcOH (45.1 mg, 751 μ mol, 42.9 μ L, 1.00 *eq*) at -10 °C. After stirring for 1 hour, NaBH₃CN (142 mg, 2.25 mmol, 3.00 *eq*) was added into the mixture. The mixture was stirred at -10 °C for 1 hour. After completion, the mixture was poured into saturated NH₄Cl aq (20 mL). The resulting mixture was extracted with DCM (2 $\times$ 30 mL). The combined organic phase was concentrated under vacuum then was purified by Prep-HPLC (Instrument: gx-I; Column: Agela DuraShell 150mm_25mm_5 μ m; Condition: water (0.05% ammonia hydroxide v/v)-ACN; Begin B:55; End B: 85; Gradient Time(min):10; 100%B Hold Time(min): 3; FlowRate(ml/min): 25) to give 1-[2-(4-bromophenoxy)ethyl]-N-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine **43** (44.0 mg, 96.2 μ mol, 13 % yield, 90.8 % purity) as yellow oil. LCMS [M+1]: 417.

[0358] ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.38 - 7.36 (d, *J*=8.4 Hz, 2H), 7.26 - 7.20 (m, 2H), 7.12 - 7.11 (m, 1H), 7.04 - 7.02 (d, *J*=7.6 Hz, 2H), 6.87 - 6.84 (d, *J*=8.8 Hz, 2H), 4.10 - 4.07 (t, *J*=5.6 Hz, 2H), 3.03 - 3.00 (d, *J*=11.6 Hz, 2H), 2.79 - 2.76 (t, *J*=5.6 Hz, 2H), 2.66 (m, 1H), 2.31 - 2.30 (m, 1H), 2.21 - 2.15 (t, *J*=12.7 Hz, 2H), 1.93 - 1.87 (m, 3H), 1.53 - 1.48 (m, 2H), 1.07 - 1.01 (m, 2H).

EXAMPLE 13

1-(3-Phenoxypropyl)-N-((trans)-2-phenylcyclopropyl)piperidin-4-amine (**46**)

Scheme 13



46: Example 13

Step 1. 1-(3-Phenoxypropyl)piperidin-4-one (**45**).

[0359] A suspension of the phenoxypropyl bromide (**44**) (0.3 mL, 1.90 mmol, d = 1.365), piperidone hydrochloride hydrate (0.44 g, 2.86 mmol), K₂CO₃ (1.05 g, 7.62 mmol), anhydrous Na₂SO₄ (0.54 g, 3.81 mmol) and KI (47 mg, 0.286 mmol) in MeCN (20 mL) was stirred at

reflux conditions for 2.5 hrs. The mixture was cooled to RT, diluted with water and extracted with EA. The extract was dried over Na₂SO₄, filtered, concentrated and the residue was purified by flash column chromatography, eluent 5% MeOH in EA, to afford title compound 45 (0.45 g, quant. yield) as oil.

[0360] ¹H NMR: 500 MHz, CDCl₃, δ (ppm): 7.30-7.26 (m, 2H), 6.96-6.90 (m 3H), 4.06 (t, *J* = 6.3 Hz, 2H), 2.78 (t, *J* = 6.1 Hz, 4H), 2.66 (t, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 6.8 Hz, 4H), 2.04-1.99 (m, 2H). MS: 233.3 (calcd.), 234.1 (M+H⁺, found).

Step 2. 1-(3-Phenoxypropyl)-N-((trans)-2-phenylcyclopropyl)piperidin-4-amine (46)

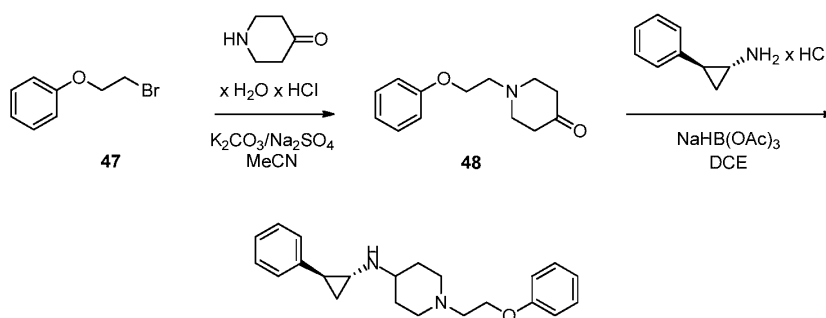
[0361] A suspension of ketone **45** (0.49 g, 2.10 mmol) and (trans)-2-phenylcyclopropanamine hydrochloride (0.43 g, 2.52 mmol) in DCE (15 mL) was stirred at RT for 2.0 hrs, cooled to 0°C then treated with the borohydride (0.80 g, 7.78 mmol). The mixture was allowed to warm to RT and stirred over 4 hrs, diluted with DCM and washed with conc. NaHCO₃ solution. The organic phase was further washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash chromatography, eluent 5 then 10% MeOH in DCM (MeOH contained 2% ammonia) to form title compound **46** (0.29 g, 39% yield) as honey-like material.

[0362] ¹H NMR: 500 MHz, CD₃OD, δ (ppm): 7.29-7.23 (m, 4H), 7.16-7.05 (m, 1H), 7.08-7.05 (m, 2H), 6.94-6.90 (m, 3H), 4.03 (t, *J* = 6.2 Hz, 2H), 3.02 (bd, *J* = 11.7, 2H), 2.73-2.67 (m, 1H), 2.60-2.57 (m, 2H), 2.36-2.33 (m, 1H), 2.16-2.10 (m, 2H), 2.03-1.90 (m, 5H), 1.56-1.48 (m, 2H), 1.11-1.03 (m, 2H). MS: 350.5 (calcd.), 351.1 (M+H⁺, found).

EXAMPLE 14

1-(2-Phenoxyethyl)-N-((trans)-2-phenylcyclopropyl)piperidin-4-amine (49)

Scheme 14



49: Example 14

Step 1. 1-(2-Phenoxyethyl)piperidin-4-one (48).

[0363] A suspension of the phenoxyethyl bromide (47) (0.30 g, 1.49 mmol), piperidone hydrochloride hydrate (0.34 g, 2.24 mmol), K₂CO₃ (0.83 g, 5.97 mmol), anhydrous Na₂SO₄ (0.42 g, 2.98 mmol) and KI (37 mg, 0.224 mmol) in MeCN (15 mL) was stirred at reflux conditions for 2.5 hrs. The mixture was cooled to RT, diluted with water and extracted with EA. The extract was dried over Na₂SO₄, filtered, concentrated and the residue was subjected to flash chromatography, eluent 5% MeOH in DCM, to afford title compound 48 (0.20 g, 60% yield) as a liquid.

[0364] ¹H NMR: 500 MHz, CDCl₃, δ (ppm): 7.31-7.28 (m, 2H), 6.98-6.91 (m 3H), 4.15 (t, *J* = 5.6 Hz, 2H), 2.95 (t, *J* = 5.6 Hz, 2H), 2.91 (t, *J* = 6.1 Hz, 4H), 2.49 (t, *J* = 6.3 Hz, 4H). MS: 219.3 (calcd.), 219.9 (M+H⁺, found).

Step 2. 1-(2-Phenoxyethyl)-N-((trans)-2-phenylcyclopropyl)piperidin-4-amine (49)

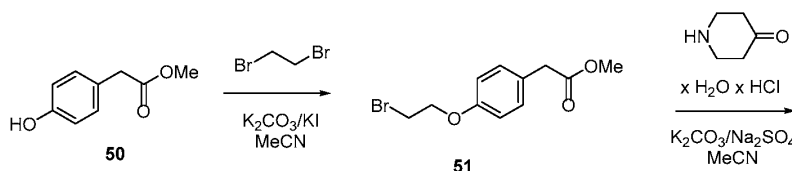
[0365] A suspension of ketone 48 (0.19 g, 0.866 mmol) and (trans)-2-phenylcyclopropanamine hydrochloride (0.18 g, 1.04 mmol) in DCE (10 mL) was stirred at RT for 2.0 hrs, cooled to 0°C then treated with the borohydride (0.33 g, 1.56 mmol). The mixture was allowed to warm to RT and stirred over 4 hrs. The mixture was then diluted with DCM and washed with conc. NaHCO₃ solution. The organic phase was further washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash chromatography, eluent 5 then 10% MeOH in DCM (MeOH contained 2% ammonia) afford title compound 49 (0.19 g, 65% yield) as honey-like material.

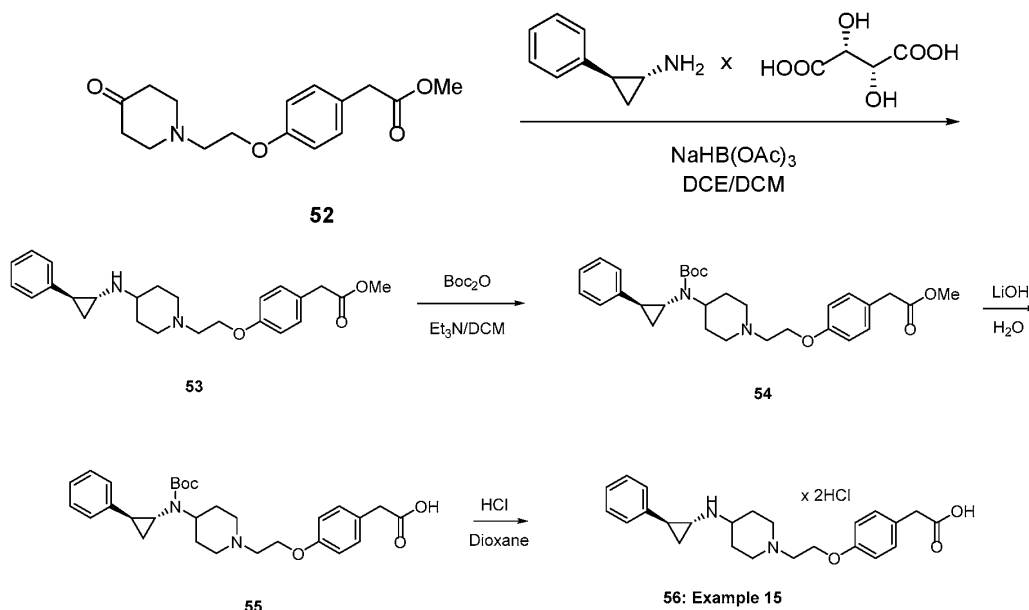
[0366] ¹H NMR: 500 MHz, CD₃OD, δ (ppm): 7.30-7.23 (m, 4H), 7.16-7.12 (m, 1H), 7.07-7.05 (m, 2H), 6.96-6.92 (m, 3H), 4.14 (t, *J* = 5.7 Hz, 2H), 3.07 (bd, *J* = 12.2, 2H), 2.83 (t, *J* = 5.6 Hz, 2H), 2.73-2.67 (m, 1H), 2.36-2.33 (m, 1H), 2.27-2.19 (m, 2H), 2.01-1.90 (m, 3H), 1.58-1.50 (m, 2H), 1.11-1.03 (m, 2H). MS: 336.5 (calcd.), 337.1 (M+H⁺, found).

EXAMPLE 15

2-(4-(2-(4-(((1R,2S)-2-Phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid dihydrochloride (56)

Scheme 15





Step 1. Methyl 2-(4-(2-bromoethoxy)phenyl)acetate (**51**).

[0367] A suspension of methyl 2-(4-hydroxyphenyl)acetate (**50**) (5.0 g, 30.1 mmol), 1,2-dibromoethane (16 mL, 186 mmol, d = 2.18), K₂CO₃ (11.50 g, 84.4 mmol) and KI (200 mg, 1.20 mmol) in MeCN (90 mL) was stirred at reflux conditions for 24 hrs. The mixture was diluted with water and extracted with EA. The extract was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum at 40°C. The resultant oil was further kept in a higher vacuum at 60°C to possibly remove the excess of dibromoethane then purified by flash chromatography, eluent DCM-hexanes (1:1) then EA-hexanes (8:17) to afford title compound **51** (5.05 g, 62% yield).

[0368] ¹H NMR: 500 MHz, CDCl₃, δ (ppm): 7.20 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.28 (t, *J* = 6.3 Hz, 2H), 3.69 (s, 3H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.53 (s, 2H).

Step 2. Methyl 2-(4-(2-(4-oxopiperidin-1-yl)ethoxy)phenyl)acetate (**52**).

[0369] A suspension of the bromide **51** (5.05 g, 18.49 mmol), piperidone hydrochloride hydrate (4.54 g, 29.6 mmol), K₂CO₃ (10.22 g, 74.0 mmol), anhydrous Na₂SO₄ (5.25 g, 37.0 mmol) and KI (153 mg, 0.924 mmol) in MeCN (100 mL) was stirred at reflux conditions for 18 hrs. The mixture was cooled to RT, diluted with water and extracted with EA. The extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography, eluent 10% MeOH in DCM (MeOH contained 2% ammonia) to afford title compound **52** (5.19 g, 96% yield) as oil.

[0370] ¹H NMR: 500 MHz, CD₃OD, δ (ppm): 7.19 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.13 (t, *J* = 5.6 Hz, 2H), 3.68 (s, 3H), 3.56 (s, 2H), 2.93 (t, *J* = 5.6 Hz, 2H), 2.89 (t, *J* = 6.1 Hz, 4H), 2.48 (t, *J* = 6.2 Hz, 4H). MS: 291.3 (calcd.), 292.0 (M+H⁺, found).

Step 3. Methyl 2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetate (53).

[0371] A suspension of ketone **52** (2.5 g, 8.58 mmol), (1R, 2S)-2-phenylcyclopropanamine (2R, 3R)-tartaric acid salt (3.16 g, 11.16 mmol) and a few drops of 6N HCl solution in a solvent mixture DCE (10 mL) and DCM (5 mL) was stirred at RT for 3.0 hrs, cooled to 0°C then treated with the borohydride (3.27 g, 15.45 mmol). The mixture was allowed to warm to RT and stirred over 14 hrs. The mixture was then diluted with DCM and washed with a NaHCO₃ solution. The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash chromatography, eluent 10% MeOH in DCM (MeOH contained 2% ammonia to afford title compound **53** (1.65 g, 47% yield) as honey-like material whose estimated purity was ca 90%. The material was taken to the next step without additional purification. MS: 408.5 (calcd.), 409.0 (M+H⁺, found).

Step 4. Methyl 2-(4-(2-(4-((tert-butoxycarbonyl)((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetate (54).

[0372] To a solution of amine **53** (1.65 g, 4.04 mmol) in DCM (20 mL) was added TEA (1.69 mL, 12.12 mmol, d = 0.726). The mixture was cooled by an ice-bath then treated with a solution of the Boc-anhydride (1.763 g, 8.08 mmol) in DCM (20 mL). The mixture was stirred at 0-5°C for 30 min then at ambient temperature for 4 hrs, diluted with DCM, washed with diluted brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography, eluent EA-hexanes (1:1) to afford title compound **54** (1.50 g, 73% yield) as honey-like material. The material contained some residual EA.

[0373] ¹H NMR: 500 MHz, CD₃OD, δ (ppm): 7.29-7.25 (m, 2H), 7.22-7.14 (m, 5H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.13 (t, *J* = 5.6 Hz, 2H), 3.78-3.71 (m, 1H), 3.69 (s, 3H), 3.60 (s, 2H), 3.17-3.09 (m, 2H), 2.82 (t, *J* = 5.6 Hz, 2H), 2.64-2.61 (m, 1H), 2.28-2.12 (m, 4H), 2.06-2.03 (m, 1H), 1.85-1.82 (m, 1H), 1.78-1.75 (m, 1H), 1.46-1.42 (m, 10H), 1.28-1.24 (m, 1H). MS: 508.7 (calcd.), 509.2 (M+H⁺, found).

Step 5. 2-(4-(2-(4-((tert-Butoxycarbonyl)((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid (55).

[0374] To a solution of ester **54** (1.50 g, 2.95 mmol) in 70% aqueous EtOH (35 mL) was added a solution of LiOH x H₂O (0.25 g, 5.90 mmol) in water (9 mL). The reaction mixture was stirred at rt for 1 hr, acidified with HCl to pH 5-6 then evaporated to its maximum. The residue

was treated with brine and extracted with DCM. The extract was dried over anhydrous Na_2SO_4 , filtered and the filtrate was evaporated to form foam which was let dry in vacuum overnight to afford title compound **55** (1.42 g, 97% yield). The material was used in the next step with no additional purification. MS: 494.6 (calcd.), 495.2 ($\text{M}+\text{H}^+$, found).

Step 6. 2-(4-(2-(4-(((1R,2S)-2-Phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid di-hydrochloride (**56**)

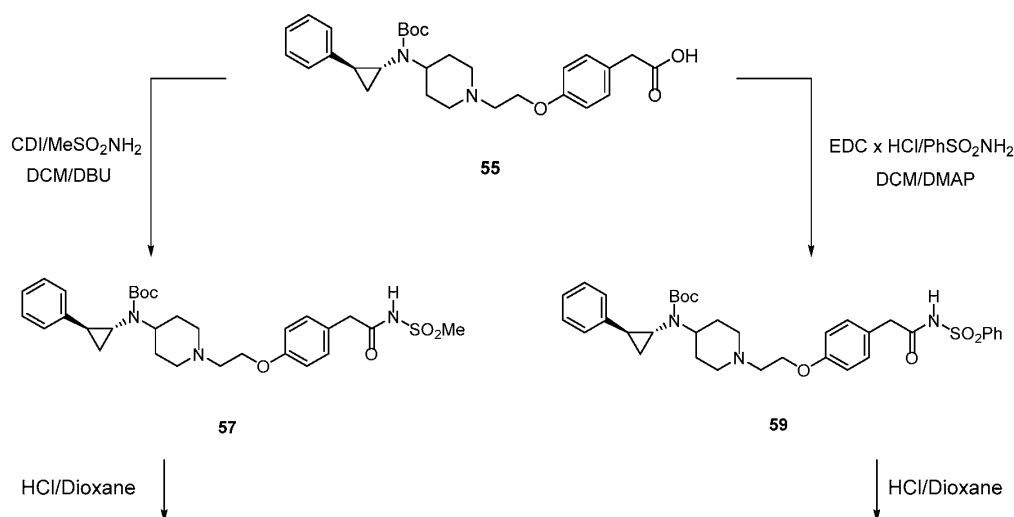
[0375] A 4M solution of HCl in dioxane (2 ml, 8.00 mmol) was added to a suspension of the compound **55** (0.200 g, 0.404 mmol) in dioxane (2 mL) at rt and the reaction mixture was stirred at ambient temperature for 3 hrs. The mixture was evaporated to dryness and the resultant white precipitate was triturated with a mixture of MeOH and acetone, collected by filtration and dried to afford title compound **56** (0.17 g, 90% yield) as white solid.

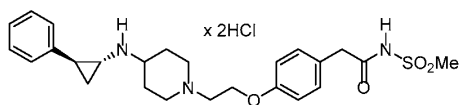
[0376] ^1H NMR: 500 MHz, $\text{DMSO}-d_6$, δ (ppm): 12.25 (bs, 1H), 10.74 (bs, 1H), 9.99 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 5H), 6.94 (d, $J = 8.6$ Hz, 2H), 4.37 (bt, 2H), 3.66 (bs, 2H), 3.50 (s, 2H), 3.46 (bs, 3H), 3.46 (bs, 2H), 2.96 (bs, 1H), 2.58-2.54 (m, 1H), 2.31 (bs, 2H), 2.10 (bs, 2H), 1.60-1.56 (m, 1H), 1.31-1.27 (m, 1H). MS: 394.5 (calcd.), 395.0 ($\text{M}+\text{H}^+$, found).

EXAMPLES 16 and 17

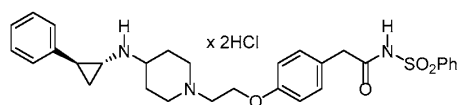
N-(Methylsulfonyl)-2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide di-hydrochloride (**58**) and
2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-*N*-(phenylsulfonyl)acetamide di-hydrochloride (**60**)

Scheme 16





58: Example 16



60: Example 17

Step 1. *tert*-Butyl (1-(2-(4-(2-(methylsulfonylamido)-2-oxoethyl)phenoxy)ethyl)piperidin-4-yl)((1R,2S)-2-phenylcyclopropyl)carbamate (**57**).

[0377] To a solution of acid **55** (200 mg, 0.404 mmol) in DCM (5 mL) at 0°C was added CDI (72 mg, 0.445 mmol). The reaction mixture was stirred for 5 min at 0°C, then for another hour at ambient temperature. To the mixture were added methyl sulfonamide (42 mg, 0.445 mmol) and the DBU (0.121 mL, 0.809 mmol, d = 1.018). The combined mixture was stirred overnight, diluted with more DCM and washed with 10% aqueous NaH₂PO₄ solution then brine. The organic phase was dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography, eluent 10, then 15% MeOH in DCM (MeOH contained 2% ammonia) to afford title compound **57** (0.208 mg, 90% yield) as off-white solid.

[0378] ¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 7.27-7.24 (m, 2H), 7.17-7.10 (m, 5H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.06 (t, *J* = 5.7 Hz, 2H), 3.61-3.54 (m, 1H), 3.47 (s, 2H), 3.14 (s, 3H), 3.07-3.03 (m, 2H), 2.77 (bt, 2H), 2.59-2.56 (m, 1H), 2.23-2.16 (m, 2H), 2.08-1.99 (m, 2H), 1.93-1.85 (m, 1H), 1.72-1.64 (m, 2H), 1.35-1.32 (m, 10H), 1.22-1.18 (m, 1H). MS: 571.7 (calcd.), 572.2 (M+H⁺, found).

Step 2. *N*-(Methylsulfonyl)-2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide di-hydrochloride (**58**).

[0379] A 4M solution of HCl in dioxane (3 mL, 12 mmol) was added to a solution of compound **57** (205 mg, 0.359 mmol) in dioxane (2 mL) at rt. The mixture was stirred at ambient temperature for 3 hrs, evaporated to dryness and the resultant white precipitate was triturated with a mixture of acetone and MeOH, collected by filtration and dried to afford title compound **58** (146 mg, 75% yield) as a white solid.

[0380] ¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 11.92 (bs, 1H), 10.65 (bs, 1H), 9.91 (bs, 2H), 7.33-7.30 (m, 2H), 7.24-7.18 (m, 5H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.37 (bt, 2H), 3.67 (bs, 2H), 3.55 (s, 2H), 3.46 (bs, 3H), 3.22 (s, 3H), 3.12 (bs, 2H), 2.97 (bs, 1H), 2.55 (bs, 1H), 2.30 (bs, 2H), 2.08 (bs, 2H), 1.57 (bs, 1H), 1.32-1.28 (m, 1H). MS: 471.6 (calcd.), 472.1 (M+H⁺, found).

Step 1. *tert*-Butyl (1-(2-(4-(2-oxo-2-(phenylsulfonylamido)ethyl)phenoxy)ethyl)piperidin-4-yl)((1R,2S)-2-phenylcyclopropyl)carbamate (**59**).

[0381] To a solution of the acid **55** (200 mg, 0.404 mmol) and benzene sulfonamide (95 mg, 0.607 mmol) in DCM (7 mL) was added EDC x HCl (155 mg, 0.809 mmol) and DMAP (99 mg,

0.809 mmol) at RT. The reaction mixture was stirred at the same conditions overnight, diluted with more DCM then washed with a NaHCO₃ solution, water and brine. The organic phase was dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography, eluent 10 % MeOH in DCM (MeOH contained 2% ammonia). The material required a second purification by flash chromatography, eluent 5% MeOH (with 2% ammonia) in DCM to afford title compound **59** (86 mg, 34% yield) as white solid. MS: 633.8 (calcd.), 634.2 (M+H⁺, found).

Step 2. 2-(4-(2-(4-(((1R,2S)-2-Phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-N-(phenylsulfonyl)acetamide di-hydrochloride (**60**).

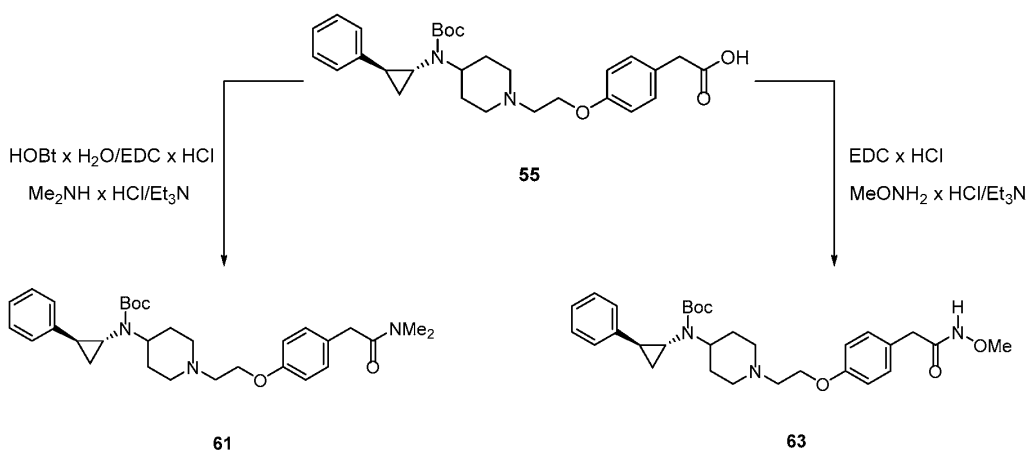
[0382] A 4M solution of HCl in dioxane (1.0 ml, 4 mmol) was added to a solution of compound **59** (86 mg, 0.136 mmol) in dioxane (1.5 mL) at rt. The mixture was stirred at ambient temperature for 3 hrs, evaporated to dryness and the resultant white solid was triturated with acetone, collected by filtration, re-dissolved in water, frozen and freeze-dried to afford title compound **60** (59 mg, 72% yield) as white solid.

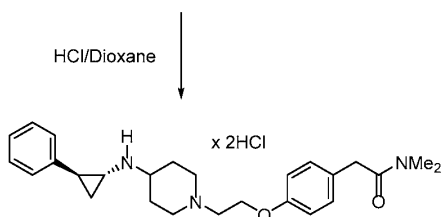
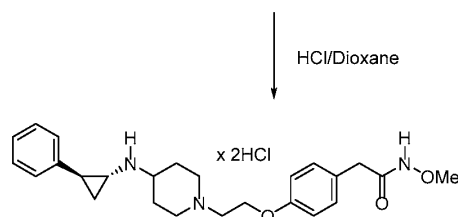
[0383] ¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 12.35 (bs, 1H), 10.73 (bs, 1H), 9.97 (bs, 2H), 7.90-7.88 (m, 2H), 7.72-7.69 (m, 1H), 7.62-7.59 (m, 2H), 7.33-7.29 (m, 2H), 7.24-7.18 (m, 3H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.35 (bt, 2H), 3.64 (bd, 2H), 3.50 (s, 2H), 3.44 (bs, 3H), 3.10 (bs, 2H), 2.96 (bs, 1H), 2.55 (bs, 1H), 2.29 (bs, 2H), 2.09 (bs, 2H), 1.59 (bs, 1H), 1.31-1.27 (m, 1H). MS: 533.7 (calcd.), 534.2 (M+H⁺, found).

EXAMPLES 18 and 19

N,N-Dimethyl-2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide d-hydrochloride (**62**) and *N*-methoxy-2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide (**64**)

Scheme 17



**62: Example 18****64: Example 19**

Step 1. *tert*-Butyl (1-(2-(4-(2-(dimethylamino)-2-oxoethyl)phenoxy)ethyl)piperidin-4-yl)((1*R*,2*S*)-2-phenylcyclopropyl)carbamate (61**).**

[0384] To a solution of acid **55** (200 mg, 0.404 mmol) in DMF (4 mL) were added HOBT x H₂O (124 mg, 0.809 mmol) followed by EDC x HCl (233 mg, 1.213 mmol). The reaction mixture was stirred at RT over 2 hrs. Then Me₂NH x HCl (165 mg, 2.200 mmol) was added followed by TEA (0.282 mL, 2.022 mmol, d = 0.726). The resultant mixture was stirred overnight then diluted with brine. A gummy precipitate was formed which was collected by filtration and re-dissolved in acetone. The solution was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography, eluent 5% MeOH in DCM (MeOH contained 2% ammonia) to afford title compound **61** (144 mg, 68% yield) as glass-like solid. MS: 521.7 (calcd.), 522.3 (M+H⁺, found).

Step 2. *N,N*-Dimethyl-2-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide d-hydrochloride (62**).**

[0385] A 4M solution of HCl in dioxane (2 mL, 8 mmol) was added to a solution of compound **61** (144 mg, 0.276 mmol) in dioxane (2 mL) at rt. The mixture was stirred at ambient temperature for 3 hrs, evaporated to dryness and the resultant yellowish gummy precipitate was dissolved in MeOH and filtered. The filtrate was evaporated almost completely and treated with excess acetone. A white precipitate was formed which was collected by filtration, re-dissolved in water, frozen and freeze-dried to afford title compound **62** (113 mg, 83% yield) as off-white solid.

[0386] ¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 10.83(bs, 1H), 10.03 (bs, 2H), 7.33-7.29 (m, 2H), 7.24-7.15 (m, 5H), 6.93 (d, *J* = 8.6 Hz, 2H), 4.37 (bt, 2H), 3.67 (bd, 2H), 3.61 (s, 2H), 3.46 (bs, 3H), 3.14 (bs, 2H), 2.98 (s, 3H), 2.97 (bs, 1H), 2.81 (s, 3H), 2.59-2.56 (m, 1H), 2.32 (bs, 2H), 2.11 (bs, 2H), 1.61-1.57 (m, 1H), 1.31-1.26 (m, 1H). MS: 421.6 (calcd.), 422.3 (M+H⁺, found).

Step 1. *tert*-Butyl 1-(2-(4-(2-(methoxyamino)-2-oxoethyl)phenoxy)ethyl)piperidin-4-yl)((1*R*,2*S*)-2-phenylcyclopropyl)carbamate (**63**).

[0387] To a solution of acid **55** (185 mg, 0.374 mmol) in DCM (5 mL) were added TEA (0.21 mL, 1.496 mmol, $d = 0.726$), EDC $\times$ HCl (143 mg, 0.748 mmol), and the $\text{NH}_2\text{OMe} \times \text{HCl}$ (66 mg, 0.785 mmol). The mixture was stirred overnight, diluted with DCM and washed with diluted brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent 5% MeOH (containing 2% ammonia) in DCM to afford title compound **63** (73 mg, 37% yield) as white foam. MS: 523.7 (calcd.), 524.2 ($\text{M}+\text{H}^+$, found).

Step 2. *N*-Methoxy-2-(4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide (**64**).

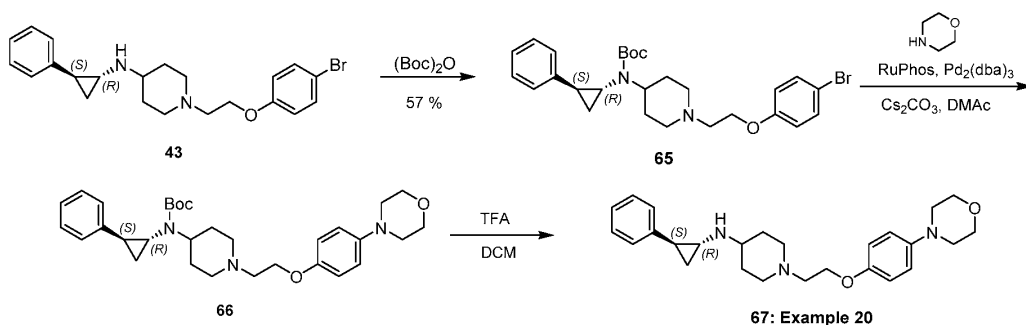
[0388] A 4M solution of HCl in dioxane (1.0 mL, 4 mmol) was added to a solution of compound **63** (73 mg, 0.139 mmol) in dioxane (1 mL) at rt. The mixture was stirred at ambient temperature for 3 hrs, evaporated to dryness and the resultant white precipitate was triturated with acetone, collected by filtration, re-dissolved in water, frozen and freeze-dried to afford title compound **64** (67 mg, 93% yield) as white solid.

[0389] ^1H NMR: 500 MHz, $\text{DMSO}-d_6$, δ (ppm): 11.34 (bs, 1H), 10.89 (bs, 1H), 10.08 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 5H), 6.94 (d, $J = 8.6$ Hz, 2H), 4.37 (bt, 2H), 3.66 (bd, 2H), 3.56 (s, 3H), 3.45 (bs, 3H), 3.23 (s, 2H), 3.14 (bs, 2H), 2.95 (bs, 1H), 2.60-2.56 (m, 1H), 2.32 (bs, 2H), 2.12 (bs, 2H), 1.62-1.58 (m, 1H), 1.30-1.26 (m, 1H). MS: 423.6 (calcd.), 424.2 ($\text{M}+\text{H}^+$, found).

EXAMPLE 20

1-[2-(4-morpholinophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (**66**)

Scheme 18



Step 1. *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (65)

[0390] A mixture of 1-[2-(4-bromophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (**43**, Example 12), (7.20 g, 17.3 mmol, 1.00 *eq*) and (Boc)₂O (7.57 g, 34.7 mmol, 7.96 mL, 2.00 *eq*) in DCM (10.0 mL) was stirred at 50 °C for 5 hours. After completion, the mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE/EA from 10/1 to 0/1) to give *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl] carbamate (6.00 g, 9.89 mmol, 57 % yield, 85.0 % purity) as yellow oil which was re-purified by Prep-HPLC (Instrument: HPLC-A; Column: Phenomenex Gemini C18 250*50mm*10 um; Condition: water (0.05% ammonia hydroxide v/v)-ACN; Begin B:70; End B: 95; Gradient Time(min): 31,85%; 100%B Hold Time(min): 5; FlowRate(ml/min):80) to give *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (1.9 g purity 98.5 %) as white solid. LCMS [M+1]: 517

[0391] ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 7.42 - 7.40 (m, 2H), 7.24 - 7.22 (m, 2H), 7.15 - 7.10 (m, 3H), 6.92 - 6.90 (m, 2H), 4.23 - 4.21 (m, 2H), 3.82 - 3.79 (m, 1H), 3.42 - 3.31 (m, 2H), 3.24 - 3.22 (m, 2H), 2.67 - 2.66 (m, 2H), 2.59 (m, 1H), 2.44 - 2.17 (m, 3H), 2.12 - 2.11 (m, 1H), 1.98 - 1.84 (m, 2H), 1.40 - 1.38 (m, 9H), 1.25 - 1.22 (m, 1H)

Step 2. 1-[2-(4-morpholinophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (66)

[0392] To a solution of *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (100 mg, 194 umol, 1.00 *eq*) and morpholine (33.8 mg, 388 umol, 34.1 uL, 2.00 *eq*) in DMAC (1.00 mL) was added RuPhos (9.05 mg, 19.4 umol, 0.10 *eq*), Pd₂(dba)₃ (8.88 mg, 9.70 umol, 0.05 *eq*) and Cs₂CO₃ (190 mg, 582 umol, 3.00 *eq*). The mixture was stirred at 85 °C under N₂ for 5 hours. After completion, water (10 mL) was added into the mixture. The resulting mixture was extracted with DCM (3 × 20 mL). The combined organic phase was concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH 20/1) to give 1-[2-(4-morpholinophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (100 mg, 83.3 % purity, 82.4% yield) as yellow oil. LCMS [M+1]: 522

Step 3. 1-[2-(4-morpholinophenoxy)ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (67, Example 20)

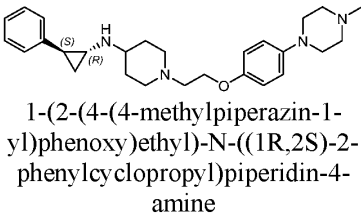
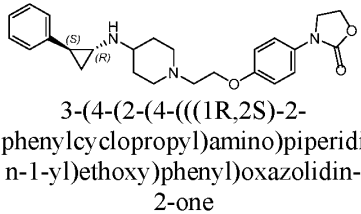
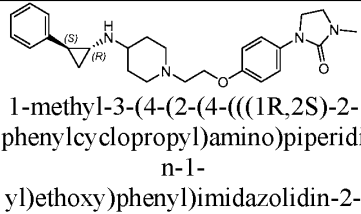
[0393] A mixture of *tert*-butyl *N*-[1-[2-(4-morpholinophenoxy)ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (100 mg, 192 umol, 1.00 *eq*) and TFA (219 mg, 1.92 mmol, 142 uL, 10.0 *eq*) in DCM (1.00 mL) was stirred at 15 °C for 1 hour. After completion, the

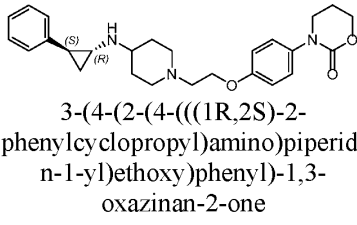
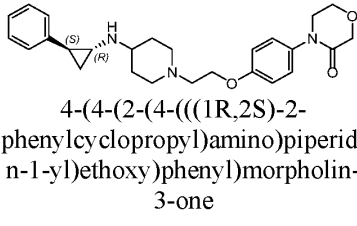
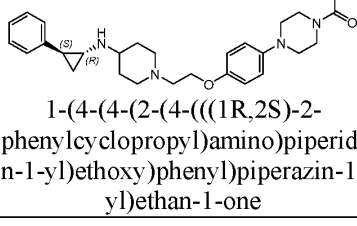
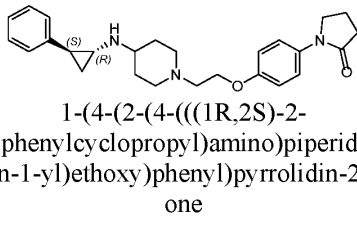
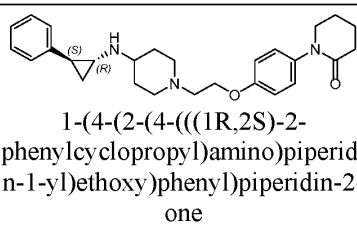
reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (Instrument: LC-E; Column: Phenomenex Synergi C18 150*30mm*4um; Condition: water (0.05% ammonia hydroxide v/v)-ACN; Begin B:1; End B: 21; Gradient Time(min):10.5; 100%B Hold Time(min): 2; FlowRate(ml/min): 25). The desired fractions were collected and lyophilized to give 1-[2-(4-morpholinophenoxy)ethyl]-N-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (40 mg, 75.34 umol, 39.30 % yield, 3 HCl) as a white solid. LCMS [M+1]: 422

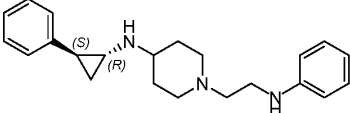
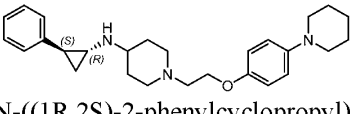
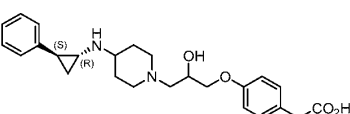
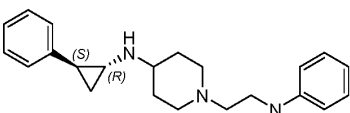
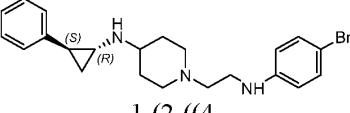
[0394] ^1H NMR (400 MHz, methanol- d_4) δ = 7.77 (d, J =8.8 Hz, 2H), 7.33 - 7.19 (m, 7H), 4.52 - 4.49 (m, 2H), 4.16 - 4.12 (m, 4H), 3.87 - 3.67 (m, 9H), 3.34 (m, 2H), 3.05 - 3.04 (m, 1H), 2.60 - 2.59 (m, 1H), 2.48 - 2.45 (m, 2H), 2.25 - 2.22 (m, 2H), 1.62 - 1.60 (m, 1H), 1.45 - 1.29 (m, 1H).

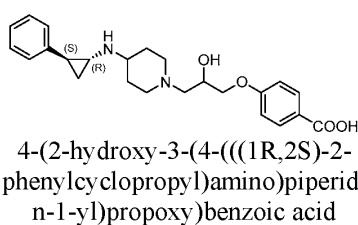
[0395] Following the teachings of the Reaction Schemes and synthetic routes set forth herein, the following compounds were prepared:

Table 1
Exemplary Compounds of Formula (I) and Formula (II)

Ex. #	Structure	Method	LCMS [M+1] Observed	^1H NMR
21	 1-(2-(4-(4-methylpiperazin-1-yl)phenoxy)ethyl)-N-((1 <i>R</i> ,2 <i>S</i>)-2-phenylcyclopropyl)piperidin-4-amine	Example 20	435.2	(400 MHz, METHANOL- d_4) δ = 7.42 - 7.40 (m, 2H), 7.24 - 7.22 (m, 2H), 7.15 - 7.10 (m, 3H), 6.92 - 6.90 (m, 2H), 4.23 - 4.21 (m, 2H), 3.82 - 3.79 (m, 1H), 3.42 - 3.31 (m, 2H), 3.24 - 3.22 (m, 2H), 2.67 - 2.66 (m, 2H), 2.59 (m, 1H), 2.44 - 2.17 (m, 3H), 2.12 - 2.11 (m, 1H), 1.98 - 1.84 (m, 2H), 1.40 - 1.38 (m, 9H), 1.25 - 1.22 (m, 1H)
22	 3-(4-(2-(4-(((1 <i>R</i> ,2 <i>S</i>)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)oxazolidin-2-one	Example 20	422.1	(400 MHz, deuterium oxide) δ = 7.40 - 7.33 (m, 4H), 7.30 - 7.26 (m, 1H), 7.17 (d, J =7.2 Hz, 2H), 7.03 (d, J =9.2 Hz, 2H), 4.59 (t, J =8.0 Hz, 2H), 4.38 - 4.37 (m, 2H), 4.08 - 4.04 (m, 2H), 3.85 - 3.69 (m, 3H), 3.65 - 3.55 (m, 2H), 3.30-3.15 (m, 2H), 2.99 - 2.96 (m, 1H), 2.52 - 2.40 (m, 3H), 2.11 - 1.95 (m, 2H), 1.54 - 1.43 (m, 2H).
23	 1-methyl-3-(4-(2-(4-(((1 <i>R</i> ,2 <i>S</i>)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)imidazolidin-2-one	Example 20	435.3	(400 MHz, deuterium oxide) δ = 7.36 - 7.28 (m, 5H), 7.17 (d, J =7.6 Hz, 2H), 6.99 (d, J =9.6 Hz, 2H), 4.36 - 4.33 (m, 2H), 3.80 - 3.71 (m, 5H), 3.63 - 3.55 (m, 2H), 3.50 - 3.46 (m, 2H), 3.26 - 3.15 (m, 2H), 2.99 - 2.97 (m, 1H), 2.78 (s, 3H), 2.50 - 2.43 (m, 3H), 2.07 - 1.93 (m, 2H), 1.52 - 1.44 (m, 2H).

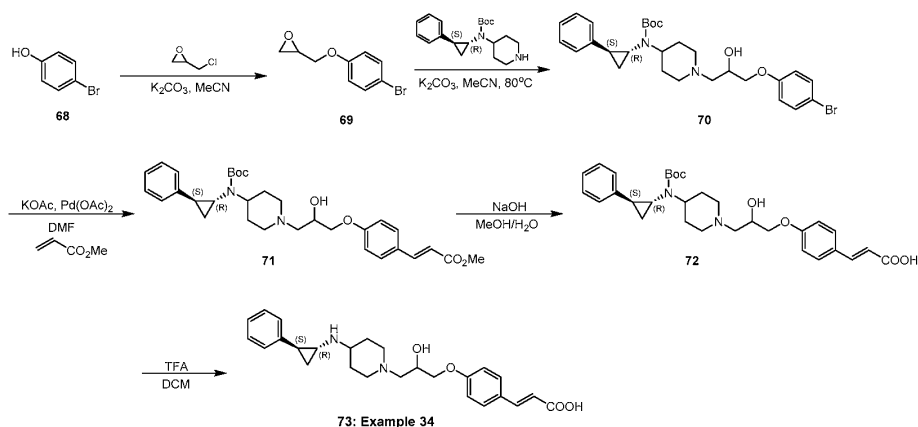
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
24	 3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one	Example 20	436.3	(400 MHz, deuterium oxide) δ = 7.31 - 7.27 (m, 2H), 7.24 - 7.20 (m, 3H), 7.11 (d, J =7.2 Hz, 2H), 6.97 (d, J =8.8 Hz, 2H), 4.37 (t, J =5.2 Hz, 2H), 4.33 - 4.31 (m, 2H), 3.78 - 3.75 (d, J =11.6 Hz, 2H), 3.70-3.60 (m, 1H), 3.59 - 3.54 (m, 4H), 3.30-3.20 (m, 2H), 2.95 - 2.91 (m, 1H), 2.45 - 2.35 (m, 3H), 2.12 - 2.06 (m, 2H), 2.04-1.90 (m, 2H), 1.48 - 1.35 (m, 2H).
25	 4-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)morpholin-3-one	Example 20	436.2	(400 MHz, deuterium oxide) δ = 7.32 - 7.27 (m, 2H), 7.25 - 7.23 (m, 3H), 7.15 (d, J =7.2 Hz, 2H), 7.03 (d, J =8.8 Hz, 2H), 4.37 - 4.35 (m, 2H), 4.29 (s, 2H), 4.02 (t, J =4.8 Hz, 2H), 3.85-3.77 (m, 2H), 3.75 - 3.65 (m, 3H), 3.60 - 3.55 (m, 2H), 3.23 - 3.15 (m, 2H), 2.97 - 2.93 (m, 1H), 2.48 - 2.41 (m, 3H), 2.05 - 1.95 (m, 2H), 1.50 - 1.42 (m, 2H).
26	 1-(4-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)piperazin-1-yl)ethan-1-one	Example 20	463.4	(400 MHz, deuterium oxide) δ = 7.56 - 7.36 (d, J =8.8 Hz, 2H), 7.36 - 7.33 (m, 2H), 7.29 - 7.25 (m, 1H), 7.18 - 7.14 (m, 4H), 4.45 - 4.38 (m, 2H), 4.05 - 3.95 (m, 4H), 3.83 - 3.62 (m, 9H), 3.23 - 3.15 (m, 2H), 3.01 - 2.95 (m, 1H), 2.55 - 2.44 (m, 3H), 2.17 (s, 3H), 2.10 - 1.95 (m, 2H), 1.55 - 1.40 (m, 2H).
27	 1-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)pyrrolidin-2-one	Example 20	420.4	(400 MHz, deuterium oxide) δ = 7.37 - 7.33 (m, 4H), 7.32 - 7.28 (m, 1H), 7.18 - 7.16 (d, J =7.6 Hz, 2H), 7.04 - 7.02 (d, J =8.4 Hz, 2H), 4.38 - 4.36 (m, 2H), 3.84 - 3.82 (m, 4H), 3.77 - 3.68 (m, 1H), 3.63 - 3.55 (m, 2H), 3.25-3.13 (m, 2H), 3.00 - 2.97 (m, 1H), 2.57 (t, J =8.0 Hz, 2H), 2.50 - 2.40 (m, 3H), 2.17 - 2.11 (m, 2H), 2.08 - 1.95 (br. s., 2H), 1.52 - 1.44 (m, 2H).
28	 1-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)piperidin-2-one	Example 20	434.2	(400 MHz, D ₂ O) δ = 7.36 - 7.33 (m, 2H), 7.29 - 7.27 (m, 1H), 7.19 - 7.15 (m, 4H), 7.03 (d, J =8.8 Hz, 2H), 4.37 (br. s., 2H), 3.83 (d, J =12.4 Hz, 2H), 3.90-3.80 (m, 1H), 3.65 - 3.55 (d, J =4.0 Hz, 4H), 3.25-3.10 (m, 2H), 3.03 - 2.95 (m, 1H), 2.55 - 2.40 (m, 5H), 2.10-1.95 (br. s., 2H), 1.95-1.80 (m, 4H), 1.55 - 1.42 (m, 2H).

Ex. #	Structure	Method	LCMS [M+] Observed	¹ H NMR
29	 1-(2-(phenylamino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 12	336.0	(400MHz, methanol-d ₄) δ 7.48 - 7.38 (m, 2H), 7.37 - 7.31 (m, 2H), 7.30 - 7.24 (m, 3H), 7.24 - 7.18 (m, 3H), 3.92 - 3.81 (m, 4H), 3.81 - 3.71 (m, 1H), 3.60 - 3.48 (m, 2H), 3.32 - 3.24 (m, 2H), 3.06 (td, J=3.6, 7.2 Hz, 1H), 2.60 - 2.55 (m, 1H), 2.52 - 2.41 (m, 2H), 2.31 - 2.14 (m, 2H), 1.65 - 1.55 (m, 1H), 1.52 - 1.41 (m, 1H).
30	 N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(4-(piperidin-1-yl)phenoxy)ethyl)piperidin-4-amine	Example 20	420.0	(400 MHz, chloroform-d) δ = 7.27 - 7.23 (m, 2H), 7.20 - 7.15 (m, 1H), 7.02 (d, J=7.6 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 6.82 (d, J=9.2 Hz, 2H), 4.06 (t, J=6.0 Hz, 2H), 3.72 (q, J=6.8 Hz, 1H), 3.05 - 2.95 (m, 5H), 2.80 (t, J=5.6 Hz, 2H), 2.73 - 2.60 (m, 1H), 2.41 - 2.30 (m, 1H), 2.25 - 2.10 (m, 2H), 1.93 - 1.74 (m, 3H), 1.73 - 1.69 (m, 2H), 1.56 - 1.53 (m, 3H), 1.50 - 1.40 (m, 2H), 1.27 - 1.23 (m, 2H), 1.07 (m, 1H), 1.00 - 0.98 (m, 1H).
31	 2-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acetic acid	Example 7	425.2	(400 MHz, methanol-d ₄) δ = 7.35 - 7.31 (m, 2H), 7.27 - 7.18 (m, 5H), 6.94 - 6.91 (d, J=8.8 Hz, 2H), 4.42 - 4.40 (m, 1H), 4.05 - 3.99 (m, 2H), 3.92 - 3.80 (m, 2H), 3.75 - 3.65 (m, 1H), 3.55 (s, 2H), 3.46 - 3.35 (m, 2H), 3.30 - 3.15 (m, 2H), 3.03 - 3.01 (m, 1H), 2.54 - 2.52 (m, 1H), 2.48 - 2.39 (m, 2H), 2.20 - 2.05 (m, 2H), 1.58 - 1.56 (m, 1H), 1.48 - 1.45 (m, 1H).
32	 1-(2-(methyl(phenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 12	350.2	(400MHz, methanol-d ₄) δ 7.54 - 7.46 (m, 2H), 7.44 - 7.40 (m, 2H), 7.38 - 7.28 (m, 2H), 7.25 - 7.23 (m, 1H), 7.23 - 7.17 (m, 3H), 4.05 (t, J=6.8 Hz, 2H), 3.90 - 3.70 (m, 3H), 3.45 - 3.40 (m, 2H), 3.30 - 3.25 (m, 2H), 3.28 (s, 3H), 3.10 - 3.04 (m, 1H), 2.60 - 2.55 (m, 1H), 2.54 - 2.45 (m, 2H), 2.25 - 2.17 (m, 2H), 1.65 - 1.58 (m, 1H), 1.47 - 1.43 (m, 1H)
33	 1-(2-((4-bromophenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 12	416.1	(400 MHz, methanol-d ₄) δ 7.50 (d, J=8.8 Hz, 2H), 7.38 - 7.18 (m, 5H), 7.11 (d, J=8.8 Hz, 2H), 3.93 - 3.67 (m, 5H), 3.55 - 3.52 (m, 2H), 3.26 - 3.22 (m, 2H), 3.11 - 3.02 (m, 1H), 2.63 - 2.59 (m, 1H), 2.53 - 2.47 (m, 2H), 2.29 - 2.16 (m, 2H), 1.70 - 1.57 (m, 1H), 1.49 - 1.45 (m, 1H)

Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
34	 4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)benzoic acid	Example 7	411.4	(400 MHz, D ₂ O) δ = 7.94 - 7.93 (d, <i>J</i> =8.8 Hz, 2H), 7.37 - 7.34 (m, 2H), 7.30 - 7.26 (m, 1H), 7.18 (d, <i>J</i> =7.2 Hz, 2H), 7.01 (d, <i>J</i> =8.8 Hz, 2H), 4.48 - 4.46 (m, 1H), 4.17 - 4.09 (m, 2H), 3.85 - 3.38 (m, 3H), 3.48 - 3.35 (m, 2H), 3.32 - 3.05 (m, 2H), 3.02 - 2.95 (m, 1H), 2.52 - 2.40 (m, 3H), 2.13 - 2.95 (m, 2H), 1.54 - 1.45 (m, 2H).

EXAMPLE 35

(*E*)-3-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylic acid (**73**)

Step 1. 2-[(4-bromophenoxy)methyl]oxirane

[0396] To a mixture of 4-bromophenol (10.0 g, 57.8 mmol, 2.00 eq) and 2-(chloromethyl)oxirane (12.9 g, 140 mmol, 11.0 mL, 4.85 eq) in MeCN (200 mL) was added K₂CO₃ (11.9 g, 86.7 mmol, 3.00 eq) in one portion. The mixture was stirred at 90 °C for 12 hours. After completion, the mixture was concentrated, diluted with DCM (150 mL), then washed with H₂O (150 mL). The organic phase was washed with brine (150 mL × 2), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=100/1~50/1) to give 2-[(4-bromophenoxy)methyl]oxirane (9.10 g, crude) as white solid

[0397] ¹H NMR (400 MHz, chloroform-*d*) δ 7.46 - 7.36 (m, 1H), 6.88 - 6.79 (m, 1H), 4.25 - 4.22 (m, 1H), 3.95 - 3.91 (m, 1H), 3.41 - 3.31 (m, 1H), 3.00 - 2.87 (m, 1H), 2.82 - 2.72 (m, 1H).

Step 2. *tert*-butyl *N*-[1-[3-(4-bromophenoxy)-2-hydroxy-propyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate

[0398] To a mixture of 2-[(4-bromophenoxy)methyl]oxirane (3.00 g, 13.10 mmol, 1.00 *eq*) and *tert*-butyl *N*-[(1*R*,2*S*)-2-phenylcyclopropyl]-*N*-(4-piperidyl)carbamate (4.56 g, 14.4 mmol, 1.10 *eq*) in MeCN (50.0 mL) was added K₂CO₃ (3.62 g, 26.2 mmol, 2.00 *eq*), and the reaction was stirred at 85 °C for 12 hours. After completion, the reaction was added water (80 mL), then extracted with EA (60 mL × 2), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1-3/1) to give the product *tert*-butyl *N*-[1-[3-(4-bromophenoxy)-2-hydroxy-propyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (5.50 g, 9.79 mmol, 74.7 % yield, 97.1 % purity) as yellow solid. LCMS [M+1]: 545,547

[0399] ¹H NMR (400 MHz, chloroform-*d*) δ 7.29 (d, *J*=8.8 Hz, 2H), 7.24 - 7.17 (m, 2H), 7.15 - 7.07 (m, 1H), 7.01 (d, *J*=7.2 Hz, 2H), 6.73 (d, *J*=8.8 Hz, 2H), 4.02 - 3.91 (m, 1H), 3.88 - 3.85 (m, 2H), 3.70 - 3.39 (m, 2H), 3.07 - 2.92 (m, 1H), 2.85 - 2.78 (m, 1H), 2.57 - 2.36 (m, 3H), 2.35 - 2.21 (m, 1H), 2.14 - 1.83 (m, 4H), 1.77 - 1.61 (m, 2H), 1.47 - 1.24 (m, 10H), 1.21 - 1.14 (m, 1H).

Step 3. (*E*)-3-[4-[3-[4-[*tert*-butoxycarbonyl]-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]-2-hydroxy-propoxy]phenyl]prop-2-enoate

[0400] Compound 71: To a mixture of *tert*-butyl *N*-[1-[3-(4-bromophenoxy)-2-hydroxy-propyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (800 mg, 1.47 mmol, 1.00 *eq*) and methyl prop-2-enoate (470 mg, 5.46 mmol, 489 uL, 3.71 *eq*) in DMF (15.0 mL) was added KOAc (158 mg, 1.61 mmol, 1.10 *eq*), Pd(OAc)₂ (32.9 mg, 147 umol, 0.10 *eq*) and *tris*-*o*-tolylphosphane (44.6 mg, 147 umol, 0.10 *eq*), the reaction was stirred at 120 °C for 12 hours. After completion, the reaction was added water (30 mL), extracted with EA (25 mL × 2), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1~1/1) to give the product (*E*)-3-[4-[3-[4-[*tert*-butoxycarbonyl]-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]-2-hydroxy-propoxy]phenyl]prop-2-enoate (400 mg, 719 umol, 48.9 % yield, 99% purity) as yellow oil. LCMS [M+1]: 551

Step 4. (*E*)-3-[4-[3-[4-[*tert*-butoxycarbonyl]-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]-2-hydroxy-propoxy]phenyl]prop-2-enoic acid

[0401] To a mixture of methyl (*E*)-3-[4-[3-[4-[*tert*-butoxycarbonyl]-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]-2-hydroxy-propoxy]phenyl]prop-2-enoate (200 mg, 363 umol, 1.00 *eq*) in MeOH (3.00 mL) and H₂O (1.00 mL) was added NaOH (58.1 mg, 1.45 mmol,

4.00 eq), and the reaction was stirred at 15 °C for 12 hours. After completion, the reaction was added water (10 mL), then extracted with DCM (15 mL × 2), the combined organic layers were dried over Na₂SO₄, filtered and concentrated to give (*E*)-3-[4-[3-[4-[*tert*-butoxycarbonyl]-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]-2-hydroxy-propoxy]phenyl]prop-2-enoic acid (150 mg, 254 μmol, 69.9 % yield, 90.8 % purity) as yellow solid which was used for the next step without further purification. LCMS [M+1]: 537

Step 5. E)-3-[4-[2-hydroxy-3-[4-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]propoxy]phenyl]prop-2-enoic acid

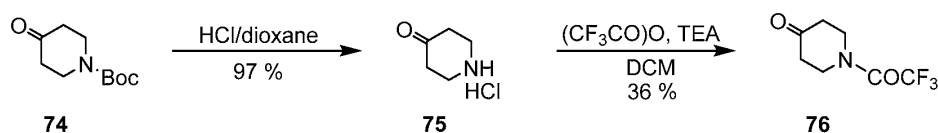
[0402] To a mixture of (*E*)-3-[4-[3-[4-[*tert*-butoxycarbonyl]-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]-2-hydroxy-propoxy]phenyl]prop-2-enoic acid (150 mg, 279 μ mol, 1.00 *eq*) in DCM (1.00 mL) was added TFA (1.54 g, 13.5 mmol, 1.00 mL, 48.3 *eq*), the reaction was stirred at 15 °C for 1 hour. After completion, the reaction was concentrated, diluted with CH₃CN (3 mL), then the mixture was adjusted with Na₂CO₃ solid to pH 6~7, the solid was filtered. The filtrate was purified by Prep-HPLC (Instrument: GX-B; Column: Welch Ultimate AQ-C18 150 * 30 mm * 5 μ m; Condition: water (0.1 % TFA)-ACN; Begin B: 20; End B: 43; Gradient Time (min): 10; 100 % B Hold Time (min): 3; FlowRate (ml/min): 25) to give (*E*)-3-[4-[2-hydroxy-3-[4-[[*(1R,2S)*-2-phenylcyclopropyl]amino]-1-piperidyl]propoxy]phenyl]prop-2-enoic acid (64.0 mg, 96.1 μ mol, 34.4 % yield, 99.8 % purity, 2 TFA) as white solid. LCMS [M+1]: 437

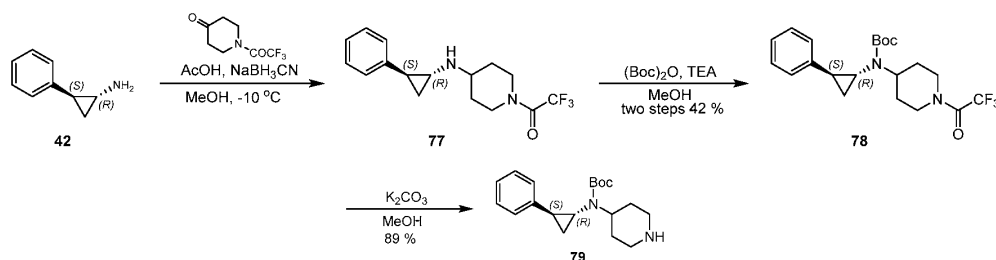
[0403] ^1H NMR (400 MHz, methanol- d_4) δ 7.64 (d, $J=16.0$ Hz, 1H), 7.60 - 7.57 (m, 2H), 7.39 - 7.31 (m, 2H), 7.30 - 7.17 (m, 3H), 7.02 (d, $J=8.8$ Hz, 2H), 6.37 (d, $J=16.0$ Hz, 1H), 4.46 - 4.42 (m, 1H), 4.16 - 4.03 (m, 2H), 3.88 - 3.84 (m, 2H), 3.75 - 3.69 (m, 1H), 3.41 - 3.48 (m, 2H), 3.32 - 3.15 (m, 2H), 3.03 - 3.01 (m, 1H), 2.58 - 2.35 (m, 3H), 2.25 - 2.01 (m, 2H), 1.61 - 1.43 (m, 2H).

EXAMPLE 36

Synthesis of Intermediate 79:

tert-butyl ((1*R*, 2*S*)-2-phenylcyclopropyl)(piperidin-4-yl)carbamate





[0404] Compound **79** was prepared from compound **74** and **42**.

[0405] Compound **75**: To a mixture of *tert*-butyl 4-oxopiperidine-1-carboxylate (100 g, 502 mmol, 1.00 *eq*) in dioxane (750 mL) was added HCl/dioxane (750 mL), and the reaction was stirred at 15 °C for 12 hours. After completion, the precipitated solid was filtered, washed with dioxane (400 mL), then the solid was dried under vacuum. The product piperidin-4-one (66.0 g, 487 mmol, 97.0 % yield, HCl) was obtained as white solid.

[0406] ¹H NMR (400 MHz, Deuterium oxide) δ 3.20 (t, *J* = 5.8 Hz, 4H), 1.92 (t, *J* = 5.8 Hz, 4H)

[0407] Compound **76**: To a mixture of **75** (66.0 g, 487 mmol, 1.00 *eq*, HCl) in DCM (600 mL) was added TEA (197 g, 1.95 mol, 270 mL, 4.00 *eq*) and (CF₃CO)₂O (307 g, 1.46 mol, 203 mL, 3.00 *eq*) dropwise at 0 °C, the mixture was stirred at 0 - 15 °C for 12 hours under N₂. After completion, the reaction mixture was washed with water (2 × 800 mL), diluted with HCl aqueous (0.5 N, 2 × 800 mL), sat. aqueous NaHCO₃ (2 × 800 mL) successively, the organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was triturated with petroleum ether (200 mL), the precipitated solid was filtered and dried under vacuum to give 1-(2,2,2-trifluoroacetyl)piperidin-4-one (34.5 g, 177 mmol, 36.3 % yield) as yellow solid.

[0408] ¹H NMR (400 MHz, Chloroform-*d*) δ 4.01 - 3.89 (m, 4H), 2.62 - 2.56 (m, 4H)

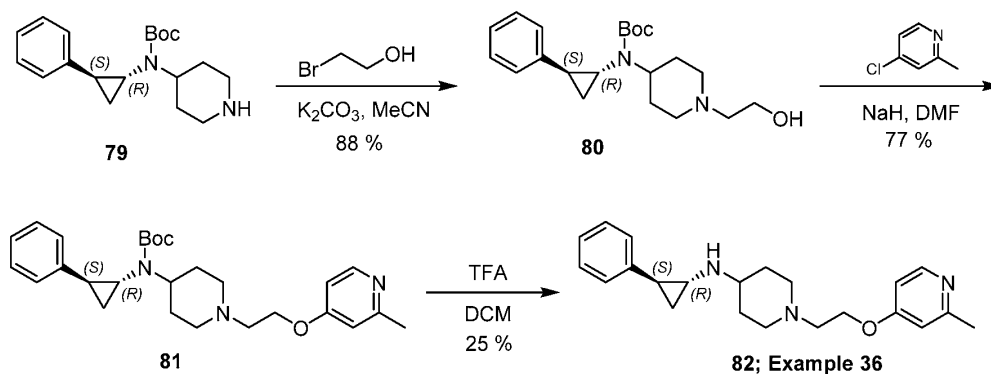
Compound **77**: To a mixture of (1*R*, 2*S*)-2-phenylcyclopropanamine (23.0 g, 173 mmol, 1.00 *eq*) and 1-(2,2,2-trifluoroacetyl)piperidin-4-one (35.4 g, 181 mmol, 1.05 *eq*) in MeOH (500 mL) was added AcOH (31.1 g, 518 mmol, 29.6 mL, 3.00 *eq*), the reaction was stirred at 15 °C for 0.5 hour, then the mixture was cooled to -10 °C and NaBH₃CN (32.6 g, 518 mmol, 3.00 *eq*) was added to the mixture, the mixture was stirred at -10 ~ 15 °C for 11.5 hours. After completion, the reaction mixture was added to H₂O (500 mL) and concentrated. The residue was extracted with DCM (2 × 400 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The product 2,2,2-trifluoro-1-[4-[(1*R*, 2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl] ethanone (59.2 g, crude) was obtained as yellow solid which was used for the next step without further purification. LCMS [*M*+1]: 313

Compound 78: To a mixture of 2,2,2-trifluoro-1-[4-[(1*R*, 2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]ethanone (59.2 g, 189 mmol, 1.00 *eq*) in MeOH (200 mL) was added (Boc)₂O (82.7 g, 379 mmol, 87.1 mL, 2.00 *eq*) and TEA (57.5 g, 568 mmol, 78.8 mL, 3.00 *eq*), the mixture was stirred at 50 °C for 12 hours. After completion, the reaction mixture was concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 5/1) to give *tert*-butyl *N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]-*N*-[1-(2,2,2-trifluoroacetyl)-4-piperidyl] carbamate (42.3 g, 79.8 mmol, 42.1 % yield, 77.8 % purity) as colorless oil. LCMS [M-99]: 313

[0409] **Compound 79:** To a mixture of *tert*-butyl *N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]-*N*-[1-(2,2,2-trifluoroacetyl)-4-piperidyl]carbamate (40.0 g, 96.9 mmol, 1.00 *eq*) in MeOH (200 mL) and H₂O (50.0 mL) was added K₂CO₃ (53.6 g, 388 mmol, 4.00 *eq*), the mixture was stirred at 15 °C for 12 hours. After completion, the reaction mixture was added water (500 mL), then extracted with DCM (3 × 400 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated to give *tert*-butyl *N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]-*N*-(4-piperidyl)carbamate (27.3 g, 65.4 mmol, 88.9 % yield, 75.8 % purity) as yellow solid. LCMS [M+1]: 317.

[0410] ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.32 - 7.22 (m, 2H), 7.19 - 7.11 (m, 3H), 3.82 - 3.73 (m, 1H), 3.16 - 3.03 (m, 2H), 2.67 - 2.57 (m, 3H), 2.16 - 2.11 (m, 1H), 2.08 - 1.71 (m, 4H), 1.46 - 1.39 (m, 10H), 1.34 - 1.20 (m, 1H).

1-[2-[(2-methyl-4-pyridyl)oxy]ethyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]piperidin-4-amine



[0411] Example 36 was prepared from compound 79:

[0412] **Compound 80:** To a solution of *tert*-butyl *N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]-*N*-(4-piperidyl)carbamate (300 mg, 948 μmol, 1.00 *eq*) and 2-bromoethanol (237 mg, 1.90 mmol, 135 μL, 2.00 *eq*) in MeCN (6.00 mL) was added K₂CO₃ (262 mg, 1.90 mmol, 2.00 *eq*). The mixture was stirred at 85 °C for 5 hours. After completion, the precipitate was filtrated off and the filtrate

was concentrated under vacuum. The residue was purified by silica gel (DCM/MeOH from 100/1 to 10/1), and the combined fractions were concentrated. *tert*-butyl *N*-[1-(2-hydroxyethyl)-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate **80** (300 mg, 798 μ mol, 84.1 % yield, 95.8 % purity) was obtained as yellow oil. LCMS [M-55]: 305

[0413] Compound **81**: To a solution of *tert*-butyl *N*-[1-(2-hydroxyethyl)-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (100 mg, 277 μ mol, 1.00 *eq*) in DMF (2.00 mL) was added NaH (22.2 mg, 555 μ mol, 60 % purity, 2.00 *eq*). After stirring at 15 °C for 1 hour, 2-methyl-4-chloropyridine (76.6 mg, 555 μ mol, 2.00 *eq*) was added. The mixture was stirred at 85 °C for 15 hours. The precipitate was filtrated off and the filtrate was concentrated under vacuum and purified by Prep-TLC (DCM/MeOH 10/1, Rf: 0.3).

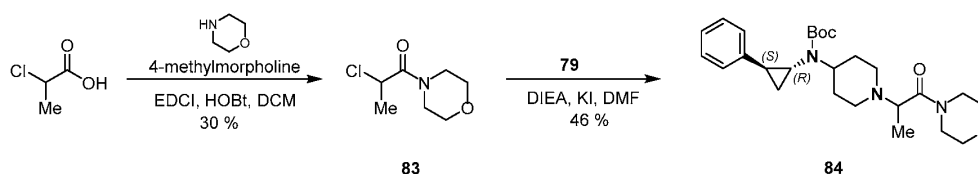
[0414] *tert*-butyl *N*-[1-[2-[(2-methyl-4-pyridyl)oxy]ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (200 mg, 213 μ mol, 76.6 % yield, 48.0 % purity) was obtained as a yellow oil. LCMS [M+1]: 452

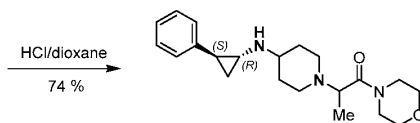
[0415] Compound **82**, Example 36: A mixture of *tert*-butyl *N*-[1-[2-[(2-methyl-4-pyridyl)oxy]ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (200 mg, 443 μ mol, 1.00 *eq*) and TFA (1.51 g, 13.3 mmol, 984 μ L, 30.00 *eq*) in DCM (2.00 mL) was stirred at 15 °C for 1 hour. After completion, the reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 35%-65%, 10min). The desired fractions were collected and lyophilized to give 1-[2-[(2-methyl-4-pyridyl)oxy]ethyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]piperidin-4-amine (39.0 mg, 111 μ mol, 25.1 % yield) as colorless oil. LCMS [M+1]: 352.

[0416] ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.19 - 8.18 (d, *J*=6 Hz, 1H), 7.23 - 7.20 (m, 2H), 7.11 (m, 1H), 7.04 - 7.02 (m, 2H), 6.86 (, 1H), 6.86 - 6.80 (m, 1H), 4.20 - 4.18 (t, *J*=5.2 Hz, 2H), 3.02 - 2.99 (br d, *J*=11.6 Hz, 2H), 2.81 - 2.79 (br t, *J*=5.6 Hz, 2H), 2.66 (m, 1H), 2.46 (s, 3H), 2.30 - 2.29 (m, 1H), 2.19 - 2.18 (m, 2H), 1.94 - 1.88 (m, 3H), 1.50 (m, 2H), 1.07 - 1.01 (m, 2H)

EXAMPLE 37

1-morpholino-2-(4-(((1*R*, 2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one





85

[0417] Compound **85**, Example 37, was prepared from 2-chloropropionic acid:

Compound **83**: *N*-Methylmorpholine (1.50 ml, 13.8 mmol), followed by 1-hydroxybenzotriazole (1.48 g, 11.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.31 g, 12.0 mmol) were added to a stirred, ice-cooled solution of 2-chloropropionic acid (1.00 g, 9.20 mmol) in dichloromethane (30.0 ml). The resulting solution was stirred at about 0° C for 45 minutes. Morpholine (2.40 ml, 27.6 mmol) was then added, the cooling bath removed and the reaction mixture stirred at 20 °C for 12 hrs. The residue was partitioned between ethyl acetate (50.0 mL) and water (30.0 mL), then the separated organic phase and washed with brine (30.0 mL), dried over sodium sulfate, and evaporated under reduced pressure to give a residue. The residue was purified by prep-TLC (dichloromethane/Methanol 10/1) to give 2-chloro-1-morpholinopropan-1-one (500 mg, 2.81 mmol, 30.5 % yield) as colorless oil.

[0418] ¹H NMR (400 MHz, methanol-*d*₄) δ = 4.91 (q, *J* = 6.4 Hz, 1H), 3.75 - 3.50 (m, 8H), 1.62 (d, *J* = 6.4 Hz, 3H).

[0419] Compound **84**: To a solution of 2-chloro-1-morpholino-propan-1-one (100 mg, 562 umol, 1.00 *eq.*) in DMF (5.00 mL) was added DIEA (291 mg, 2.25 mmol, 393 uL, 4.00 *eq.*), *tert*-butyl *N*-[1-[(1*R*, 2*S*)-2-phenylcyclopropyl]-*N*-(4-piperidyl)carbamate (356 mg, 1.13 mmol, 2.00 *eq.*) and potassium iodide (18.6 mg, 112 umol, 0.20 *eq.*). The reaction mixture was stirred at 50 °C for 12 hrs. Then the reaction mixture was partitioned between water (30.0 mL) and ethyl acetate (50.0 mL). The organic phase was separated, washed with brine (30.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate **1/1**) to give *tert*-butyl *N*-[1-[(1*R*)-1-methyl-2-morpholino-2-oxo-ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (120 mg, 262 umol, 46.5 % yield) as a white solid. LCMS [M+1]:458.

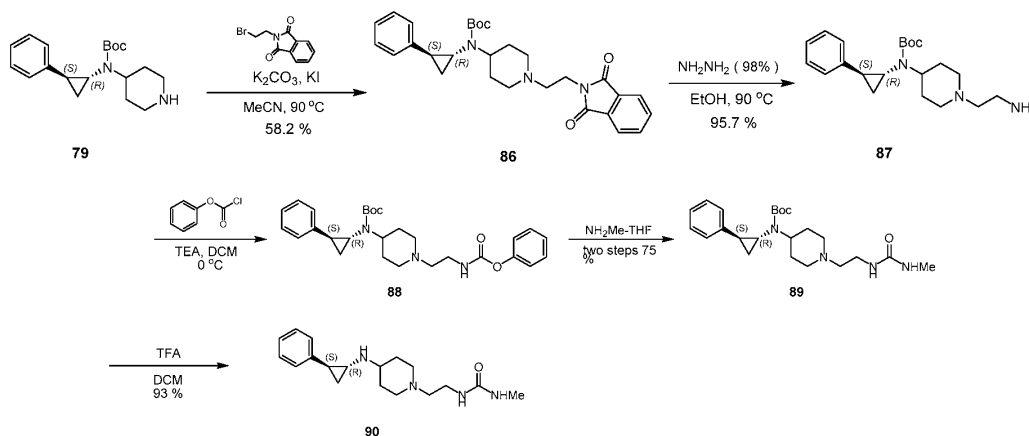
[0420] Compound **85**: A solution of *tert*-butyl *N*-[1-[(1*R*)-1-methyl-2-morpholino-2-oxo-ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (120 mg, 262 umol, 1.00 *eq.*) in HCl/dioxane (4 M, 2 mL) was stirred at 0 °C for 2 hrs. A white solid was formed. The reaction mixture was filtered and the filter cake was concentrated to give (2*R*)-1-morpholino-2-[4-[(1*R*,

2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]propan-1-one (70.0 mg, 195 μ mol, 74.7 % yield) as a white solid. LCMS [M+1]:358.

[0421] ^1H NMR (400MHz, methanol- d_4) δ = 7.37 - 7.30 (m, 2H), 7.29 - 7.17 (m, 3H), 4.61 (br d, J = 6.4 Hz, 1H), 3.93 (br d, J = 10.8 Hz, 1H), 3.81 - 3.50 (m, 10H), 3.31 - 3.17 (m, 2H), 3.09 - 3.01 (m, 1H), 2.66 - 2.37 (m, 3H), 2.31 - 1.99 (m, 2H), 1.67 - 1.59 (m, 1H), 1.57 (d, J = 6.4Hz, 3H), 1.52 - 1.37 (m, 1H).

EXAMPLE 38

1-methyl-3-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)urea



[0422] **Compound 90**, Example 38, was prepared from compound **79**.

[0423] **Compound 86**: To a mixture of *tert*-butyl *N*-[(1*R*,2*S*)-2-phenylcyclopropyl]-*N*-(4-piperidyl)carbamate (5.00 g, 15.8 mmol, 1.00 *eq.*) and 2-(2-bromoethyl)isindoline-1,3-dione (6.02 g, 23.7 mmol, 1.50 *eq.*) in acetonitrile (50.0 mL) was added potassium carbonate (8.74 g, 63.2 mmol, 4.00 *eq.*) and potassium iodide (263 mg, 1.58 mmol, 0.1 *eq.*), and then warmed to reflux at 90 °C for 18 hrs. Once complete, the reaction mixture was concentrated in vacuo to remove the solvent, water (40 mL) was added, and the aqueous layer extracted with DCM (50.0 mL $\times$ 3). The combined organic fractions were dried over anhydrous sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate 10:1 to 2:1) to give *tert*-butyl (1-(2-(1,3-dioxoisindolin-2-yl)ethyl)piperidin-4-yl)((1*R*,2*S*)-2-phenylcyclopropyl)carbamate (4.50 g, 9.19 mmol, 58.2 % yield) as a yellow oil.

[0424] ^1H NMR (400 MHz, CD_3Cl) δ = 7.88 - 7.81 (m, 2H), 7.76 - 7.69 (m, 2H), 7.24 - 7.12 (m, 3H), 7.06 - 7.01 (m, 2H), 3.85 - 3.75 (m, 2H), 3.74 - 3.62 (m, 1H), 3.12 - 2.94 (m, 2H), 2.67 - 2.55 (m, 2H), 2.54 - 2.47 (m, 1H), 2.12 - 2.06 (m, 2H), 1.95 (dq, J = 3.6, 12.0 Hz, 1H), 1.83

(dq, $J = 4.0, 12.0$ Hz, 1H), 1.77 - 1.70 (m, 1H), 1.66 (br s, 2H), 1.40 (s, 9H), 1.37 - 1.30 (m, 1H), 1.20 (q, $J = 6.4$ Hz, 1H).

[0425] Compound **87**: To a solution of *tert*-butyl *N*-[1-[2-(1, 3-dioxoisindolin-2-yl)ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (4.40 g, 8.99 mmol, 1.00 *eq.*) in ethanol (50.0 mL) was added hydrazine monohydrate (4.59 g, 89.9 mmol, 4.46 mL, 98.0 % purity, 10.0 *eq.*). The mixture was stirred at 90 °C for 1 hr. Once complete, the reaction mixture was concentrated in vacuo to remove the solvent; water (50 mL) was added and the aqueous phase extracted with ethyl acetate (40.0 mL $\times$ 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give *tert*-butyl (1-(2-aminoethyl)piperidin-4-yl)((1*R*, 2*S*)-2-phenylcyclopropyl)carbamate (3.40 g, 8.61 mmol, 95.7 % yield, 91 % purity) as a light-yellow oil. LCMS [$M+1$]: 360

[0426] Compound **88**: To a mixture of *tert*-butyl *N*-[1-(2-aminoethyl)-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (200 mg, 556 μ mol, 1.00 *eq.*) in DCM (10 mL) was added TEA (169 mg, 1.67 mmol, 231 μ L, 3.00 *eq.*) and a solution of phenyl carbonchloridate (104 mg, 668 μ mol, 83.6 μ L, 1.20 *eq.*) in DCM (5 mL). The reaction was stirred at -10 - 0 °C for 3 hours under N₂. After completion, the reaction was diluted with DCM (10 mL), then washed with H₂O (3 $\times$ 25 mL), the organic layer was dried over Na₂SO₄, filtered and concentrated to give the product *tert*-butyl *N*-[1-[2-(phenoxy carbonylamino)ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (200 mg, crude) as yellow solid which was used for the next step without further purification.

[0427] Compound **89**: A mixture of *tert*-butyl *N*-[1-[2-(phenoxy carbonylamino)ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (200 mg, 417 μ mol, 1.00 *eq.*) in methylamine (2 M, 4.62 mL, 22.1 *eq.*) (in THF) was stirred at 15 °C for another 3 hours under N₂. After completion, the reaction was diluted with DCM (15 mL), then washed with H₂O (3 $\times$ 20 mL), the organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC (Dichloromethane:Methanol=10:1). The product *tert*-butyl *N*-[1-[2-(methylcarbamoylamino)ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (130 mg, 312 μ mol, 74.8 % yield, 100 % purity) was obtained as white solid. LCMS [$M+1$]: 417

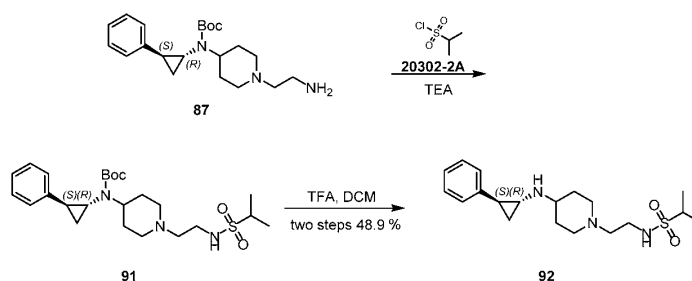
[0428] Compound **90**: To a mixture of *tert*-butyl *N*-[1-[2-(methylcarbamoylamino)ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (130 mg, 312 μ mol, 1.00 *eq.*) in DCM (1.00 mL) was added TFA (1.54 g, 13.5 mmol, 1.00 mL, 43.3 *eq.*), and the reaction was stirred at 15 °C for 1 hour. After completion, the reaction was concentrated, diluted with CH₃CN (3 mL), then the mixture was adjusted with Na₂CO₃ solid to pH 7~8, and the remaining solid was removed by filtration. The filtrate was purified by prep-HPLC (Instrument: GX-A; Column:

Phenomenex Gemini 150*25mm*10um ; Condition: water (0.05% ammonia hydroxide v/v)-ACN; Begin B: 28; End B: 50; Gradient Time (min): 10; 100%B Hold Time (min): 2; FlowRate (ml/min): 25), the obtained product was concentrated and then lyophilized to give 1-methyl-3-[2-[4-[[[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]ethyl]urea (92.7 mg, 291 umol, 93.2 % yield, 99.2 % purity) as colorless oil. LCMS [M+1]: 317

[0429] ¹H NMR (400 MHz, Methanol-d₄) δ 7.27 - 7.17 (m, 2H), 7.13 - 7.08 (m, 1H), 7.07 - 6.99 (m, 2H), 3.24 (t, *J*=6.6 Hz, 2H), 2.94 - 2.91 (m, 2H), 2.72 - 2.59 (m, 4H), 2.44 (t, *J*=6.8 Hz, 2H), 2.34 - 2.24 (m, 1H), 2.13 - 2.00 (m, 2H), 1.98 - 1.84 (m, 3H), 1.53 - 1.39 (m, 2H), 1.09 - 0.99 (m, 2H).

EXAMPLE 39

N-[2-[4-[[[(1*R*, 2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]ethyl]propane-2-sulfonamide



[0430] Compound **92**, **Example 39**, was prepared from compound **87**:

[0431] Compound **91**: To a mixture of *tert*-butyl *N*-[1-(2-aminoethyl)-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (500 mg, 1.39 mmol, 1.00 *eq.*) in DCM (20.0 mL) was added TEA (422 mg, 4.17 mmol, 578 uL, 3.00 *eq.*) and propane-2-sulfonyl chloride (396 mg, 2.78 mmol, 310 uL, 2.00 *eq.*) at 0 °C. The mixture was warmed to 25 °C slowly and stirred for 15 hrs at 25 °C. Once complete, the reaction mixture was poured into sat. sodium bicarbonate (30.0 mL), and extracted with DCM (40.0 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to remove solvent to give *tert*-butyl (1-(2-(1-methylethylsulfonamido)ethyl)piperidin-4-yl)((1*R*, 2*S*)-2-phenylcyclopropyl)carbamate (700 mg, crude) as an orange oil which used for the next step without further purification. LCMS [M+1]: 466

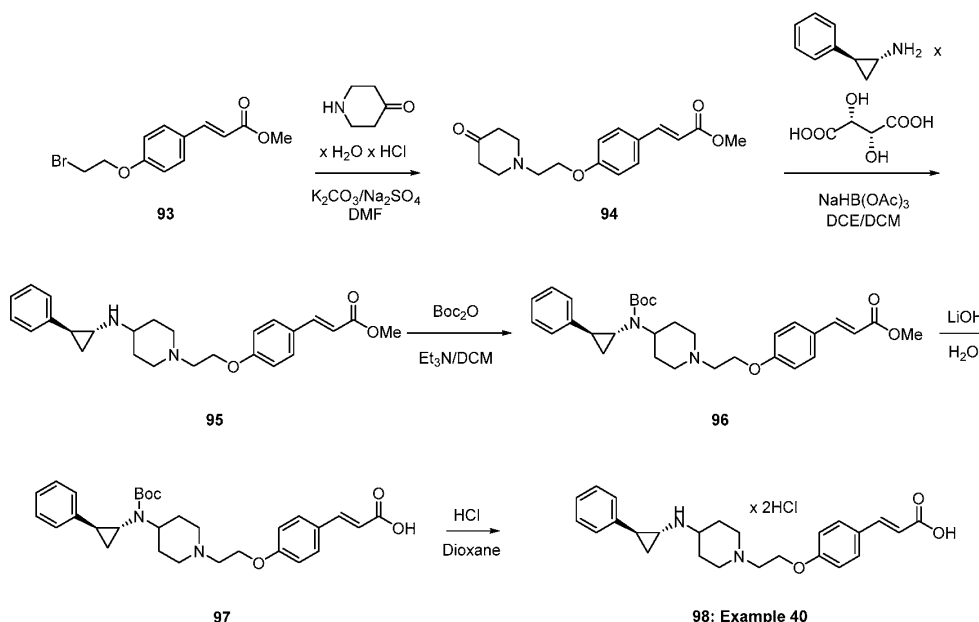
[0432] Compound **92**: To a solution of *tert*-butyl *N*-[1-[2-(isopropylsulfonylamino)ethyl]-4-piperidyl]-*N*-[(1*R*, 2*S*)-2-phenylcyclopropyl]carbamate (700 mg, 1.50 mmol, 1.00 *eq.*) in DCM (10.0 mL) was added TFA (10.0 mL) at 0 °C, and the resulting mixture was stirred for 1 hr at 0 - 25 °C. Once complete, the reaction mixture was concentrated in vacuo to remove solvent, diluted with acetonitrile (3.00 mL), and the pH was adjusted with sodium hydroxide (1 M) to pH

= 7 – 8. Solids were removed by filtration, and the residue was purified by prep-HPLC (base condition) to give compound *N*-(2-(4-(((1*R*, 2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)propane-2-sulfonamide (260 mg, 680 μ mol, two steps 48.9 % yield, 95.6 % purity) as a yellow oil. LCMS [M+1]: 366.

[0433] ^1H NMR (400 MHz, CD_3OD) δ = 7.25 - 7.18 (m, 2H), 7.14 - 7.08 (m, 1H), 7.05 - 7.00 (m, 2H), 3.29 - 3.22 (m, 1H), 3.18 (t, J = 6.8 Hz, 2H), 2.93 (d, J = 11.6 Hz, 2H), 2.64 (m, J = 4.0, 10.8 Hz, 1H), 2.50 (t, J = 6.8 Hz, 2H), 2.34 - 2.26 (m, 1H), 2.15 - 2.01 (m, 2H), 1.98 - 1.84 (m, 3H), 1.52 - 1.39 (m, 2H), 1.32 (d, J = 6.8 Hz, 6H), 1.10 - 0.97 (m, 2H).

EXAMPLE 40

(*E*)-3-(4-(2-(4-(((1*R*,2*S*)-2-Phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acrylic acid
(**98**)



Step 1. (*E*)-Methyl 3-(4-(2-(4-oxopiperidin-1-yl)ethoxy)phenyl)acrylate (**94**)

[0434] A suspension of (*E*)-methyl 3-(4-(2-bromoethoxy)phenyl)acrylate (**93**) (3.00 g, 10.52 mmol, described in WO 2008/033747), 4-piperidone hydrochloride hydrate (1.697 g, 11.05 mmol), K_2CO_3 (4.36 g, 31.6 mmol), KI (105 mg, 0.631 mmol) and anhydrous Na_2SO_4 (2.99 g, 21.04 mmol) in DMF (25 mL) was stirred at 90°C overnight, cooled to RT, diluted with brine and extracted with EA. The extract was washed with brine and dried over anhydrous Na_2SO_4 , filtered and evaporated. The remaining oil was purified by flash column chromatography, eluent

10% hexanes in EA then pure EA to afford title compound **94** (1.65 g, 52% yield) as a white solid.

[0435] ^1H NMR: 500 MHz, CDCl_3 , δ (ppm): 7.65 (d, $J = 16.0$ Hz, 1H), 7.48 (d, $J = 8.6$ Hz, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 6.32 (d, $J = 16.0$ Hz, 1H), 4.17 (t, $J = 5.6$ Hz, 2H), 3.79 (s, 3H), 2.95 (t, $J = 5.6$ Hz, 2H), 2.90 (t, $J = 6.1$ Hz, 4H), 2.49 (t, $J = 6.2$ Hz, 4H). MS: 303.4 (calcd.), 304.2 ($\text{M} + \text{H}^+$) and 322.1 ($\text{M} + \text{H}_2\text{O} + \text{H}^+$) (found).

Step 2. (E)-Methyl 3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acrylate (**95**)

[0436] To the suspension of the (1R, 2S)-2-phenylcyclopropanamine (2R, 3R)-tartaric acid salt (2.03 g, 7.07 mmol) and ketone **94** (1.65 g, 5.44 mmol) in a mixture of DCM (10 mL) and DCE (10 mL) were added 4A molecular sieves (2 g) and glacial AcOH (0.5 mL). The resultant mixture was stirred at RT for 6 hrs, cooled to 0°C and treated with the borohydride (2.075 g, 9.79 mmol). The mixture was stirred at 0°C for 30 min then allowed to warm to RT and stirred altogether for 18 hrs. The mixture was then diluted with DCM and filtered through a pad of celite. The filtrate was sequentially washed with a NaHCO_3 solution and brine, dried over anhydrous Na_2SO_4 , filtered, concentrated and the residue was purified by flash column chromatography, eluent 10% MeOH in DCM (MeOH contained 2% ammonia), to afford title compound **95** (1.27 g, 56% yield) as an oil which has solidified in vacuum. MS: 420.5 (calcd.), 421.2 ($\text{M} + \text{H}^+$, found).

Step 3. (E)-Methyl 3-(4-(2-(4-((tert-butoxycarbonyl)((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acrylate (**96**)

[0437] To a solution of amine **95** (1.27 g, 3.02 mmol) in DCM (10 mL) was added TEA (2.53 mL, 18.12 mmol). The mixture was cooled by an ice-bath then treated with a solution of the Boc-anhydride (2.64 g, 12.08 mmol) in DCM (15 mL). The mixture was stirred at 0-5°C for 30 min then at ambient temperature for 8 hrs, diluted with DCM, washed with water, dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography, eluent EA-hexanes (4:1) to afford title compound **96** (1.189 g, 76% yield) as a honey-like material that contains ca 0.7 M of EA (NMR). The product was taken to the next step as is.

[0438] ^1H NMR: 500 MHz, MeOD, δ (ppm): 7.64 (d, $J = 16.0$ Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 2H), 7.26-7.23 (m, 2H), 7.16-7.11 (m, 3H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.39 (d, $J = 16.0$ Hz, 1H), 4.16 (t, $J = 5.6$ Hz, 2H), 3.77 (s, 3H), 3.75-3.68 (m, 1H), 3.15-3.11 (m, 1H), 3.10-3.06 (m, 1H), 2.81 (t, $J = 5.5$ Hz, 2H), 2.62-2.59 (m, 1H), 2.25-2.09 (m, 4H), 2.06-1.98 (m, 1H), 1.82-1.79 (m,

1H), 1.76-1.72 (m, 1H), 1.43-1.39 (m, 10H), 1.25-1.21 (m, 1H). MS: 520.7 (calcd.), 521.3 (M+H⁺, found).

Step 4. (E)-3-(4-(2-(4-((tert-butoxycarbonyl)((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acrylic acid (**97**)

[0439] To a solution of ester **96** (1.189 g, 2.284 mmol) in THF (15 mL) was added a solution of LiOH x H₂O (422 mg, 10.05 mmol) in water (15 mL). The reaction mixture was stirred at rt for 48 hrs, acidified to pH 4 with HCl then evaporated to its maximum to remove the THF. The residual aqueous solution was diluted with brine and extracted with DCM. The extract was dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated in vacuum to afford title compound **97** (1.014 g, 88% yield) as a white fluffy material. MS: 506.6 (calcd.), 507.3 (M+H⁺, found).

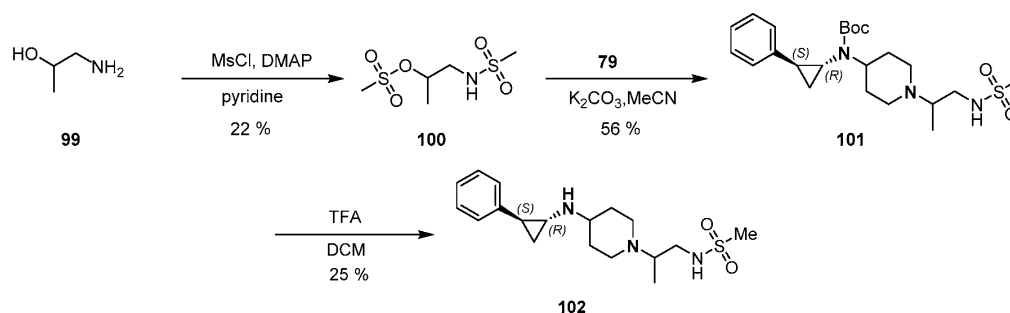
Step 5. (E)-3-(4-(2-(4-(((1R,2S)-2-Phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acrylic acid di-hydrochloride (**98**)

[0440] To a solution of compound **97** (200 mg, 0.395 mmol) in dioxane (3.0 mL) at rt was added a 4M solution of HCl in dioxane (3.0 mL, 11.84 mmol). The mixture was stirred at ambient temperature for 3 hrs, evaporated to dryness in vacuum; and the resultant white precipitate was triturated with acetone, collected by filtration and dried to afford title compound **98** (169 mg 89% yield) as a white solid.

[0441] ¹H NMR: 500 MHz, DMSO-d₆, δ (ppm): 12.25 (bs, 1H), 10.85 (bs, 1H), 10.01 (bs, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 15.9 Hz, 1H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.45 (bt, 2H), 3.68 (bs, 2H), 3.66 (bs, 1H), 3.48 (bs, 3H), 3.14 (bs, 2H), 2.97 (bs, 1H), 2.57 (m, 1H), 2.32 (bs, 2H), 2.12 (bs, 1H), 1.61-1.57 (m, 1H), 1.31-1.27 (m, 1H). MS: 406.5 (calcd.), 407.3 (M+H⁺, found).

EXAMPLE 41

N-[2-[4-[[[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]propyl]methanesulfonamide



[0442] Compound **102**, Example 41, was prepared from compound **99**:

[0443] Compound **100**: To a solution of 1-aminopropan-2-ol (1.00 g, 13.3 mmol, 1.04 mL, 1.00 eq) in pyridine (1.70 mL) was added DMAP (48.8 mg, 399 umol, 0.03 eq) at 0 °C. MsCl (3.05 g, 26.6 mmol, 2.06 mL, 2.00 eq) was added into the mixture drop-wise. The reaction mixture was stirred at 0-10 °C for 1 hour. After completion, water (10 mL) and HCl (1M, 10 mL) was added into the mixture. The resulting mixture was extracted with DCM (3×30 mL). The combined organic phase was dried with anhydrous Na₂SO₄, filtered and the filtrate was concentrated under vacuum to give [2-(methanesulfonamido)-1-methyl-ethyl] methanesulfonate (700 mg, 3.03 mmol, 22.7 % yield) as yellow oil.

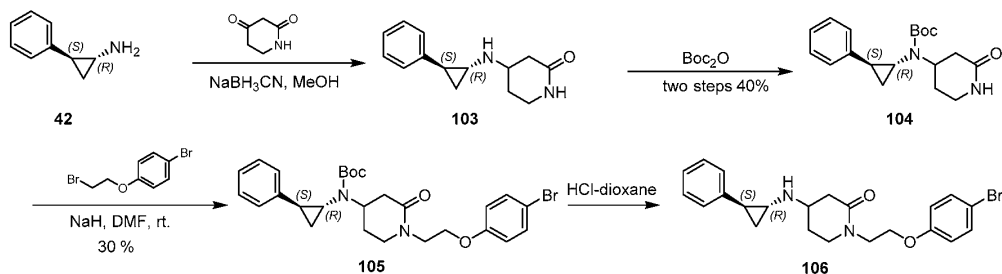
[0444] ¹H NMR (400 MHz, CHLOROFORM-d) δ = 5.13 - 5.11 (m, 1H), 4.92 - 4.87 (m, 1H), 3.48 - 3.40 (s, 1H), 3.30 - 3.32 (s, 1H), 3.09 (s, 3H), 3.02 (m, 3H), 1.46 (s, 3H).

[0445] Compound **101**: To a solution of *tert*-butyl *N*-[(1*R*,2*S*)-2-phenylcyclopropyl]-*N*-(4-piperidyl)carbamate (100 mg, 316 umol, 1.00 eq) and [2-(methanesulfonamido)-1-methyl-ethyl] methanesulfonate (73.1 mg, 316 umol, 1.00 eq) in MeCN (3.00 mL) was added K₂CO₃ (87.4 mg, 632 umol, 2.00 eq). The reaction mixture was stirred at 85 °C for 3 hours. After completion, the precipitate was filtrated off and the filtrate was concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=10/1). *tert*-Butyl *N*-[1-[2-(methanesulfonamido)-1-methyl-ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (80.0 mg, 177 umol, 56.1 % yield) was obtained as yellow oil. LCMS [M+1]: 452.

[0446] Compound **102**: To a solution of *tert*-butyl *N*-[1-[2-(methanesulfonamido)-1-methyl-ethyl]-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (50.0 mg, 111 umol, 1.00 eq) in DCM (1.00 mL) was added TFA (379 mg, 3.32 mmol, 246 uL, 30.0 eq). The reaction mixture was stirred at 25 °C for 1 hour. After completion, the reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water(0.05% HCl)-ACN]; B%: 5%-25%, 7.8min). The desired fractions were collected and lyophilized to give *N*-[2-[4-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]propyl]methanesulfonamide (12.0 mg, 28.3 umol, 25.5 % yield, 2HCl) as white solid. LCMS [M+1]: 352.

[0447] ¹H NMR (400 MHz, DEUTERIUM OXIDE) δ = 7.33 - 7.22 (m, 3H), 7.14 - 7.12 (m, 2H), 3.97 (br s, 2H), 3.67 - 3.63 (m, 2H), 3.15 (m, 3H), 3.09 (s, 3H), 2.94 (m, 1H), 2.92 (m, 1H), 2.46 - 2.39 (m, 3H), 2.08 (m, 1H), 1.93 (m, 1H), 1.48 - 1.30 (m, 2H), 1.23 (m, 3H).

EXAMPLE 42

1-[2-(4-bromophenoxy)ethyl]-4-[[*(1R,2S)*-2-phenylcyclopropyl]amino]piperidin-2-one

[0448] Compound **106**, Example 42, was prepared from compound **42**:

[0449] Compound **103**: To a mixture of piperidine-2,4-dione (84.9 mg, 751 μmol , 1.00 *eq*) in MeOH (4.00 mL) was added (*1R,2S*)-2-phenylcyclopropanamine (100 mg, 751 μmol , 1.00 *eq*) at 25 °C. After stirring at 25 °C for 1 hour, AcOH (90.2 mg, 1.50 mmol, 85.9 μL , 2.00 *eq*) was added. The resulting mixture was stirred at 25 °C for 2 hours. After completion, water (20 mL) was added into the combined mixture. The resulting mixture was extracted with DCM (3×30 mL). The combined organic phase was dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum. 4-[[*(1R,2S)*-2-phenylcyclopropyl]amino]piperidin-2-one (200 mg, crude) was obtained as yellow oil. The crude was used to the next step directly.

[0450] Compound **104**: To a solution of 4-[[*(1R,2S)*-2-phenylcyclopropyl]amino]piperidin-2-one (340 mg, 1.48 mmol, 1.00 *eq*) in MeOH (2.00 mL) was added Boc_2O (644 mg, 2.95 mmol, 678 μL , 2.00 *eq*) and Et_3N (299 mg, 2.95 mmol, 409 μL , 2.00 *eq*). The reaction mixture was stirred at 60 °C for 2 hours. After completion, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (DCM/MeOH from 50/1 to 20/1). *tert*-butyl *N*-(2-oxo-4-piperidyl)-*N*-[[*(1R,2S)*-2-phenylcyclopropyl]carbamate (200 mg, 551 μmol , 37.2 % yield, 91.0 % purity) was obtained as yellow oil. LCMS [*M*-55]: 275.

[0451] Compound **105**: To a solution of *tert*-butyl *N*-(2-oxo-4-piperidyl)-*N*-[[*(1R,2S)*-2-phenylcyclopropyl]carbamate (150 mg, 454 μmol , 1.00 *eq*) in DMF (2.00 mL) was added NaH (36.3 mg, 908 μmol , 60 % purity, 2.00 *eq*) at 0 °C. After stirring at 0 °C for 1 hour, 1-bromo-4-(2-bromoethoxy)benzene (254 mg, 908 μmol , 2.00 *eq*) was added. The reaction mixture was stirred at 0-10 °C for 1 hour. After completion, water (10 mL) was added into the mixture. The resulting mixture was extracted with DCM (3×30 mL). The combined organic phase was dried with anhydrous Na_2SO_4 , filtrated and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=10/1). *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-2-oxo-4-piperidyl]-

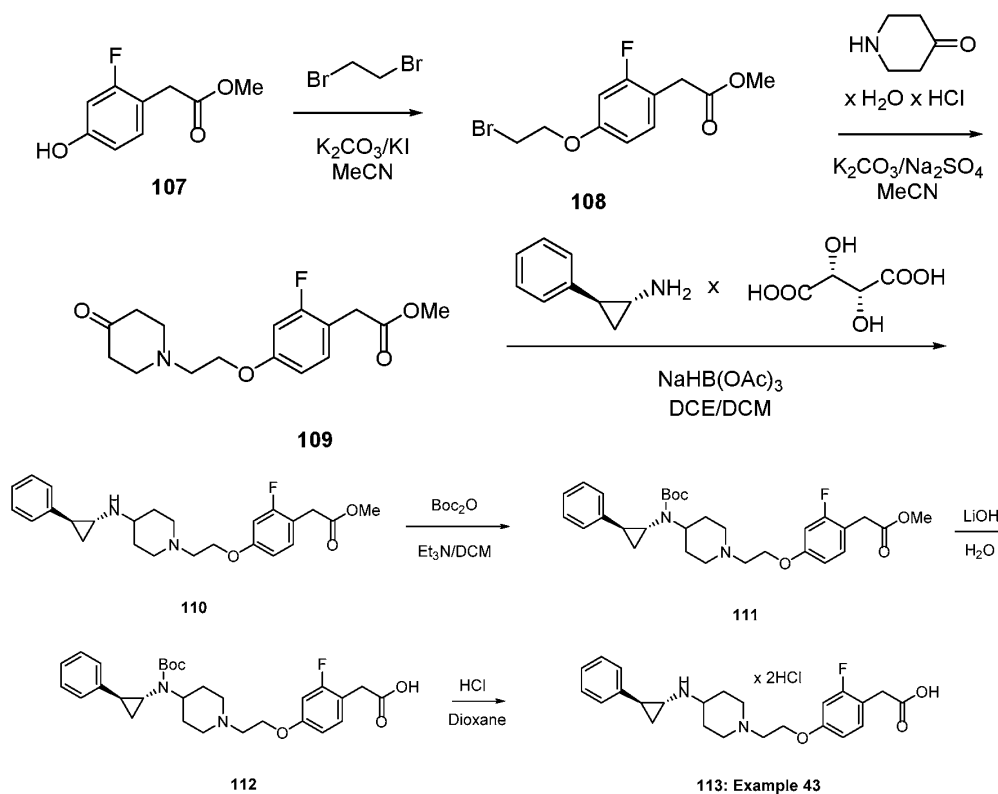
N-[*(1R,2S)*-2-phenylcyclopropyl]carbamate (40.0 mg, 75.6 μ mol, 16.6 % yield) as yellow oil. LCMS [M+1, M+3]: 529, 531.

[0452] Compound **106**: To a solution of *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-2-oxo-4-piperidyl]-*N*-[*(1R,2S)*-2-phenylcyclopropyl]carbamate (40.0 mg, 75.6 μ mol, 1.00 *eq*) in dioxane (2.00 mL) was added HCl/dioxane (4 M, 2.00 mL, 105.9 *eq*). The reaction mixture was stirred at 28 °C for 1 hour. After completion, the reaction mixture was concentrated under vacuum to give 1-[2-(4-bromophenoxy)ethyl]-4-[[*(1R,2S)*-2-phenylcyclopropyl]amino]piperidin-2-one (27.0 mg, 52.5 μ mol, 69.5 % yield, 97.6 % purity, 2HCl) as yellow solid. LCMS [M+1, M+23]: 429, 451.

[0453] ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 7.38 - 7.23 (m, 5H), 7.13 - 7.11 (m, 2H), 6.83 - 6.81 (m, 2H), 4.16 (br s, 2H), 3.70 - 3.44 (m, 5H), 2.85 - 2.83 (m, 2H), 2.45 - 2.40 (m, 2H), 2.26 (br s, 1H), 1.92 - 1.74 (m, 1H), 1.45 - 1.39 (m, 2H).

EXAMPLE 43

2-(2-Fluoro-4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid di-hydrochloride (**113**)



Step 1. Methyl 2-(4-(2-bromoethoxy)-2-fluorophenyl)acetate (**108**)

[0454] A suspension of methyl 2-(2-fluoro-4-hydroxyphenyl)acetate (**107**) (4.0 g, 21.72 mmol, WO 2012/138845), 1,2-dibromoethane (12.0 mL, 139 mmol), K₂CO₃ (8.41 g, 60.8 mmol) and KI (100 mg, 0.602 mmol) in MeCN (70 mL) was stirred for 24 hr at reflux conditions. The mixture was then cooled to RT, diluted with water and extracted with EA. The extract was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The resultant oil was subjected to flash column chromatography, eluent EA-hexanes (1:4) to afford title compound **108** (4.65 g, 74% yield) as yellowish oil.

[0455] ¹H NMR: 500 MHz, CDCl₃, δ (ppm): 7.16 (t, *J* = 8.5 Hz, 1H), 6.69-6.63 (m, 2H), 4.26 (t, *J* = 6.3 Hz, 2H), 3.70 (s, 3H), 3.62, (t, *J* = 6.2 Hz, 2H), 3.61 (s, 2H).

Step 2. Methyl 2-(2-fluoro-4-(2-(4-oxopiperidin-1-yl)ethoxy)phenyl)acetate (**109**)

[0456] A suspension of the bromide **108** (4.65 g, 15.97 mmol), piperidone hydrochloride hydrate (3.68 g, 23.96 mmol), K₂CO₃ (8.83 g, 63.9 mmol), anhydrous Na₂SO₄ (4.54 g, 31.9 mmol) and KI (265 mg, 1.597 mmol) in MeCN (90 mL) was stirred at reflux conditions for 18 hrs. The mixture was cooled to RT, diluted with water and extracted with EA. The extract was dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography, eluent 10% MeOH in DCM (MeOH contained 2% ammonia) to afford title compound **109** (4.60 g, 93% yield) as an oil.

[0457] ¹H NMR: 500 MHz, CDCl₃, δ (ppm): 7.15 (t, *J* = 8.6 Hz, 1H), 6.69-6.63 (m, 2H), 4.11 (t, *J* = 5.6 Hz, 2H), 3.70 (s, 3H), 3.60 (s, 2H), 2.92 (t, *J* = 5.6 Hz, 2H), 2.89 (t, *J* = 6.1 Hz, 4H), 2.48 (t, *J* = 6.2 Hz, 4H). MS: 309.3 (calcd.), 310.2 (M+H⁺, found).

Step 3 Methyl 2-(2-fluoro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetate (**110**)

[0458] To the suspension of (1R, 2S)-2-phenylcyclopropanamine (2R, 3R)-tartaric acid salt (3.36 g, 11.85 mmol) and ketone **109** (2.82 g, 9.12 mmol) in a mixture of DCE (20 mL) and DCM (20 mL) were added 4A molecular sieves (3 g) and glacial acetic acid (0.5 mL). The resultant mixture was stirred at RT for 16 hrs, cooled to 0°C then treated with the borohydride (3.48 g, 16.41 mmol). The mixture was stirred at 0°C for 30 min then allowed to warm to RT, stirred altogether for 3 hrs, diluted with DCM and filtered through a celite pad. The filtrate was sequentially washed with a 10% NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography, eluent 10% MeOH in DCM (MeOH contained 2% ammonia) to afford title compound **110** (4.07 g, 105% yield) as an oil. The material was taken to the next step with no extra purification. MS: 426.5 (calcd.), 427.2 (M+H⁺, found).

Step 4. Methyl 2-(4-(2-(4-((*tert*-butoxycarbonyl)((1*R*,2*S*)-2-

phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-2-fluorophenyl)acetate (**111**)

[0459] To a solution of the amine **110** (4.07 g, 9.54 mmol) in DCM (40 mL) was added TEA (4.0 mL, 28.7 mmol). The mixture was cooled by an ice-bath then treated with a solution of Boc-anhydride (4.17 g, 19.08 mmol) in DCM (40 mL). The mixture was stirred at 0-5°C for 30 min then at ambient temperature overnight, diluted with DCM, washed with dilute brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography, eluent EA-hexanes (1:1, then 4:1) to afford title compound **111** (3.72 g, 74% yield) as a honey-like material. The product contained ca 0.5 M of EA and was taken to the next step as is.

[0460] ¹H NMR: 500 MHz, CDCl₃, δ (ppm): 7.28-7.25 (m, 2H, overlaps with the residual solvent signal), 7.18-7.11 (m, 2H), 7.09-7.07 (m, 2H), 6.67-6.61 (m, 2H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.79-3.73 (m, 1H), 3.70 (s, 3H), 3.60 (s, 2H), 3.05-2.97 (m, 2H), 2.76 (t, *J* = 5.9 Hz, 2H), 2.56-2.53 (m, 1H), 2.20-2.05 (m, 4H), 1.97-1.89 (m, 1H), 1.80-1.71 (m, 2H), 1.42 (s, 9H), 1.40-1.37 (m, 1H), 1.23-1.19 (m, 1H). MS: 526.6 (calcd.), 527.4 (M+H⁺, found).

Step 5. 2-(4-(2-(4-((*tert*-Butoxycarbonyl)((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-2-fluorophenyl)acetic acid (**112**)

[0461] To a solution of ester **111** (3.72 g, 7.06 mmol) in THF (35 mL) was added a solution of LiOH hydrate (741 mg, 17.66 mmol) in 35 mL water. The reaction mixture was stirred at rt for 2 hrs, acidified to pH 6-7 then evaporated to its maximum. The residue was treated with brine and extracted with DCM. The extract was dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated to afford title compound **112** (3.57 g, 99% yield) as a white fluffy solid. MS: 512.6 (calcd.), 513.3 (M+H⁺, found).

Step 6. 2-(2-Fluoro-4-(2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid di-hydrochloride (**113**)

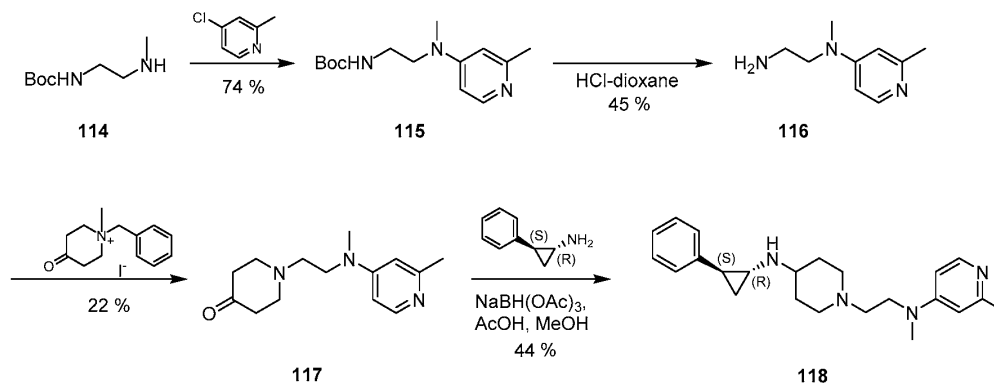
[0462] To a solution of the compound **112** (3.57 g, 6.96 mmol) in dioxane (20 mL) was added a 4M solution of HCl in dioxane (40 mL, 160 mmol) at rt. The mixture was stirred for 3 hrs, diluted with acetone and evaporated almost to completion. The resultant white precipitate was triturated with acetone, collected by filtration and dried in vacuum to afford title compound **113** (2.908 g, 86% yield) as a white solid.

[0463] ¹H NMR: 500 MHz, DMSO-*d*₆, δ (ppm): 12.39 (bs, 1H), 11.05 and 10.86 (two bs, 1H), 10.05 (bs, 2H), 7.33-7.19 (m, 6H), 6.90 (dd, *J* = 2.4 and 11.7 Hz, 1H), 6.81 (dd, *J* = 2.2 and 8.4 Hz, 1H), 4.42 (bt, 2H), 3.68 (bs, 1H), 3.66 (bs, 1H), 3.55 (s, 2H), 3.46 (bs, 3H), 3.13 (bs, 2H),

2.97 (bs, 1H), 2.58 (m, 1H), 2.33 (bs, 2H), 2.11 (bs, 2H), 1.62-1.58 (m, 1H), 1.31-1.28 (m, 1H).
MS: 412.5 (calcd.), 413.2 (M+H⁺, found).

EXAMPLE 44

N,2-dimethyl-*N*-[2-[4-[(*1R,2S*)-2-phenylcyclopropyl]amino]-1-piperidyl]ethyl]pyridin-4-amine



[0464] Compound **118**, Example 44, was prepared from compound **114**:

[0465] Compound **115**: To a solution of 4-chloro-2-methyl-pyridine (1.00 g, 7.84 mmol, 1.00 eq) and *tert*-butyl *N*-[2-(methylamino)ethyl]carbamate (1.37 g, 7.84 mmol, 1.00 eq) in DMAC (20.0 mL) was added K₂CO₃ (2.17 g, 15.7 mmol, 2.00 eq), RuPhos (366 mg, 784 μmol, 0.10 eq) and Pd₂(dba)₃ (359 mg, 392 μmol, 0.05 eq). The reaction mixture was stirred at 90 °C under N₂ for 12 hours. After completion, water (15 mL) was added into the mixture. The resulting mixture was extracted with EA (3 × 20 mL). The combined organic phase was concentrated under vacuum. The residue was purified by silica gel chromatography (DCM/MeOH from 30/1 to 5/1) to give *tert*-butyl *N*-[2-[methyl-(2-methyl-4-pyridyl)amino]ethyl]carbamate (1.80 g, 5.83 mmol, 74.3 % yield, 85.9 % purity) as yellow oil. LCMS [M+1]: 266.

[0466] ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.94 - 7.93 (d, *J* = 6.0 Hz, 1H), 6.56 - 6.54 (m, 2H), 3.52 - 3.48 (t, *J* = 6.4 Hz, 2H), 3.26 - 3.24 (m, 2H), 3.02 (s, 3H), 2.38 (s, 3H), 1.39 (s, 9H).

[0467] Compound **116**: To a mixture of *tert*-butyl *N*-[2-[methyl-(2-methyl-4-pyridyl)amino]ethyl]carbamate (1.30 g, 4.90 mmol, 1.00 eq) in MeOH (10.0 mL) was added HCl/dioxane (4.90 mmol, 10.0 mL, 1.00 eq). The reaction mixture was stirred at 25 °C for 2 hours. After completion, the reaction mixture was concentrated under vacuum. The residue was dissolve in MeOH (20 mL) and a basic ion-exchange resin was added into the mixture. The resulting mixture was stirred at 25 °C for 5 hours. The solids were removed by filtration and the

filtrate was concentrated under vacuum to give *N'*-methyl-*N'*-(2-methyl-4-pyridyl)ethane-1,2-diamine (500 mg, 2.23 mmol, 45.5 % yield, 90.0 % purity, HCl) as yellow oil.

[0468] Compound **117**: To a mixture of *N'*-methyl-*N'*-(2-methyl-4-pyridyl)ethane-1,2-diamine (1.00 g, 6.05 mmol, 1.00 *eq*) and K₂CO₃ (125 mg, 908 μ mol, 0.150 *eq*) in EtOH (14.0 mL) was added the mixture of 1-benzyl-1-methyl-1-azinan-4-one (3.01 g, 9.08 mmol, 1.50 *eq*) in H₂O (4.00 mL) at 90 °C for 0.5 hour. The reaction mixture was stirred at 90 °C for another 1 hour. After completion, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (DCM / MeOH from 30/1 to 10/1). Then purified by prep-HPLC (column: Phenomenex Synergi Max-RP 250*50mm*10 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 15%-40%, 25MIN; 69%min) to give 1-[2-[methyl-(2-methyl-4-pyridyl)amino]ethyl]piperidin-4-one (350 mg, 1.35 mmol, 22.4 % yield, 95.6 % purity) as a colorless oil. LCMS [M+1]: 248.

[0469] ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.97 - 7.95 (m, 1H), 6.56 - 6.51 (m, 2H), 3.65 - 3.55 (m, 2H), 3.07 - 3.03 (d, *J* = 16.4 Hz, 3H), 2.86 - 2.85 (m, 2H), 2.72 - 2.71 (m, 1H), 2.57 (m, 3H), 2.46 - 2.44 (m, 2H), 2.39 (s, 3H), 1.79 (m, 2H).

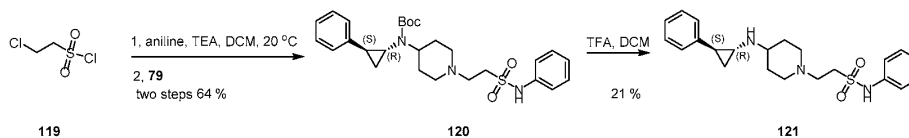
[0470] Compound **118**: To a solution of (*1R,2S*)-2-phenylcyclopropanamine (20.0 mg, 150 μ mol, 1.00 *eq*) in MeOH (3.00 mL) was added 1-[2-[methyl-(2-methyl-4-pyridyl)amino]ethyl]piperidin-4-one (44.6 mg, 180 μ mol, 1.20 *eq*) at -10 °C, then AcOH (18.0 mg, 300 μ mol, 17.2 μ L, 2.00 *eq*) was added. 1 hour later, NaBH(OAc)₃ (95.5 mg, 451 μ mol, 3.00 *eq*) was added. The reaction mixture was stirred at -10 -25 °C for 2 hours. After completion, water (10 mL) was added into the mixture. The resulting mixture was extracted with DCM (3 $\times$ 20 mL). The combined organic phase was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 μ m; mobile phase: [water(0.05%HCl)-ACN]; B%: 0%-20%, 7.8min).

[0471] The desired fraction were collected and lyophilized to give *N*,2-dimethyl-*N*-[2-[4-[[(*1R,2S*)-2-phenylcyclopropyl]amino]-1-piperidyl]ethyl]pyridin-4-amine (32.0 mg, 67.2 μ mol, 44.7 % yield, 99.5 % purity, 3HCl) as a yellow oil. LCMS [M+1]: 365.

[0472] ¹H NMR (400 MHz, D₂O) δ = 7.98 - 7.96 (d, *J* = 7.6 Hz, 1H), 7.39 - 7.35 (m, 2H), 7.32 - 7.30 (m, 1H), 7.20 - 7.18 (m, 2H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.80 - 6.79 (m, 1H), 4.01 - 3.97 (m, 2H), 3.77 - 3.74 (m, 3H), 3.46 - 3.42 (m, 2H), 3.23 (m, 2H), 3.17 (s, 3H), 3.01 - 2.99 (m, 1H), 2.52 - 2.49 (m, 6H), 2.07 - 1.94 (m, 2H), 1.55 - 1.47 (m, 2H).

EXAMPLE 45

N-phenyl-2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethanesulfonamide



[0473] Compound **121**, Example 45, was prepared from **119**:

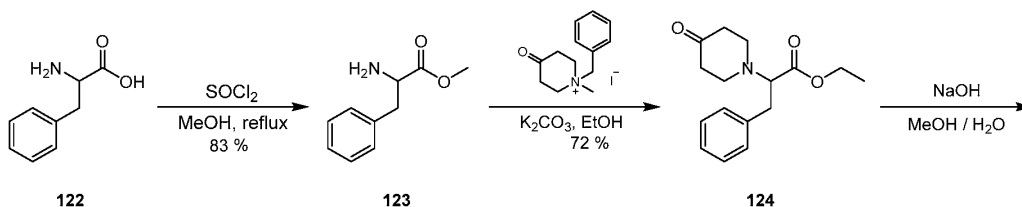
[0474] Compound **120**: To a solution of 2-chloroethanesulfonyl chloride (70.0 mg, 429 μmol , 44.8 μL , 1.00 *eq.*) in DCM (5.00 mL) was added TEA (108 mg, 1.07 mmol, 148 μL , 2.50 *eq.*) and aniline (31.9 mg, 343 μmol , 31.3 μL , 0.80 *eq.*) at 20 °C. After stirring for 2 hrs, *tert*-butyl ((1*R*, 2*S*)-2-phenylcyclopropyl)(piperidin-4-yl)carbamate (163 mg, 515 μmol , 1.20 *eq.*) was added and stirred for 0.5 hrs more. The reaction mixture was concentrated. The residue was purified by prep-TLC to give *tert*-butyl ((1*R*,2*S*)-2-phenylcyclopropyl)(1-(2-(*N*-phenylsulfamoyl)ethyl)piperidin-4-yl)carbamate (60.0 mg, 273 μmol , 63.6 % yield) as a yellow solid. LCMS [M+1]: 500.

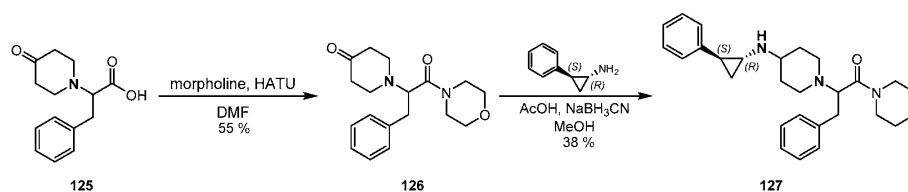
[0475] Compound **121**: To a solution of *tert*-butyl ((1*R*, 2*S*)-2-phenylcyclopropyl) (1-(2-(*N*-phenylsulfamoyl)ethyl)piperidin-4-yl)carbamate (60.0 mg, 120 μmol , 1.00 *eq.*) in DCM (3.00 mL) was added TFA (1.85 g, 16.2 mmol, 1.20 mL, 134 *eq.*) at 0 °C. Then the reaction mixture was stirred at 20 °C for 12 hr. The reaction mixture was neutralized to 7-8 with saturated sodium bicarbonate and then concentrated. The solid was removed by filtration and the filtrate was concentrated to give a residue which purified by prep-HPLC (formic acid) to give *N*-phenyl-2-(4-(((1*R*, 2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethanesulfonamide (10.0 mg, 25.0 μmol , 20.8 % yield) as a white solid. LCMS [M+1]: 400.

[0476] ^1H NMR (400 MHz, methanol-*d*₄) δ = 8.23 (br s, 2H), 7.36 - 7.29 (m, 2H), 7.27 - 7.20 (m, 4H), 7.11 (td, *J* = 7.2, 11.2 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 3.27 - 3.19 (m, 2H), 2.73 - 2.63 (m, 4H), 2.62 - 2.55 (m, 1H), 2.35 - 2.26 (m, 1H), 1.97 - 1.82 (m, 3H), 1.73 (br d, *J* = 11.2 Hz, 2H), 1.34 - 1.21 (m, 2H), 1.07 - 0.94 (m, 2H).

EXAMPLE 46

1-morpholino-3-phenyl-2-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one





[0477] Compound 127, Example 46, was prepared from compound 122.

[0478] Compound 123: To a mixture of 2-amino-3-phenyl-propanoic acid (2.00 g, 12.1 mmol, 1.00 *eq*) in MeOH (30.0 mL) was added SOCl₂ (4.32 g, 36.3 mmol, 2.63 mL, 3.00 *eq*) in portions at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hour, then the mixture was heated to 70 °C and stirred at 70 °C for 2.5 hours. After completion, the reaction mixture was concentrated. The residue was diluted with EA (30 mL), washed with sat. aq. NaHCO₃ (2 × 30 mL), the organic layer was washed with brine (2 × 30 mL), dried over Na₂SO₄, filtered and concentrated. The product methyl 2-amino-3-phenyl-propanoate (1.80 g, 10.0 mmol, 82.9 % yield) was obtained as a yellow oil.

[0479] ¹H NMR (400 MHz, Chloroform-d) δ 7.36 - 7.20 (m, 5H), 3.79 - 3.73 (m, 4H), 3.12 (dd, *J*=5.2, 13.6 Hz, 1H), 2.88 (dd, *J*=8.0, 13.6 Hz, 1H)

[0480] Compound 124: To a mixture of methyl 2-amino-3-phenyl-propanoate (1.80 g, 10.0 mmol, 1.00 *eq*) and K₂CO₃ (208 mg, 1.51 mmol, 0.15 *eq*) in EtOH (20.0 mL) was added a mixture of 1-benzyl-1-iodo-1-methyl-2,3,5,6-tetrahydropyridin-4-one (4.99 g, 15.1 mmol, 1.50 *eq*) in H₂O (10.0 mL) in portions at 78 °C, then the mixture was heated to 90 °C and stirred at 90 °C for 3 hours. After completion, the reaction mixture was diluted with water (30 mL) and extracted with EA (3 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Petroleum ether/Ethyl acetate=10/1~5/1) to give ethyl 2-(4-oxo-1-piperidyl)-3-phenyl-propanoate (2.00 g, 6.73 mmol, 67.1 % yield, 92.7 % purity) as yellow oil.

[0481] ¹H NMR (400 MHz, Chloroform-d) δ 7.33 - 7.21 (m, 5H), 4.15 - 4.07 (m, 2H), 3.63 (dd, *J*=6.8, 8.8 Hz, 1H), 3.17 - 2.97 (m, 4H), 2.95 - 2.84 (m, 2H), 2.51 - 2.37 (m, 4H), 1.19 (t, *J*=7.2 Hz, 3H)

[0482] Compound 125: To a mixture of ethyl 2-(4-oxo-1-piperidyl)-3-phenyl-propanoate (500 mg, 1.82 mmol, 1.00 *eq*) in MeOH (10.0 mL) and H₂O (2.00 mL) was added NaOH (291 mg, 7.28 mmol, 4.00 *eq*), the reaction mixture was stirred at 20 °C for 3 hours. After completion, the reaction mixture was adjusted to pH ~6, then concentrated. The solid was dissolved with MeOH (10 mL), concentrated, the residue was triturated with DCM (15 mL), the solid was

filtered and dried. The product 2-(4-oxo-1-piperidyl)-3-phenyl-propanoic acid (380 mg, 1.34 mmol, 73.6 % yield, HCl) was obtained as gray solid.

[0483] ^1H NMR (400 MHz, DMSO- d_6) δ 7.34 - 7.16 (m, 5H), 3.55 (dd, $J=6.8, 8.0$ Hz, 1H), 3.04 - 2.76 (m, 6H), 2.46 - 2.21 (m, 4H)

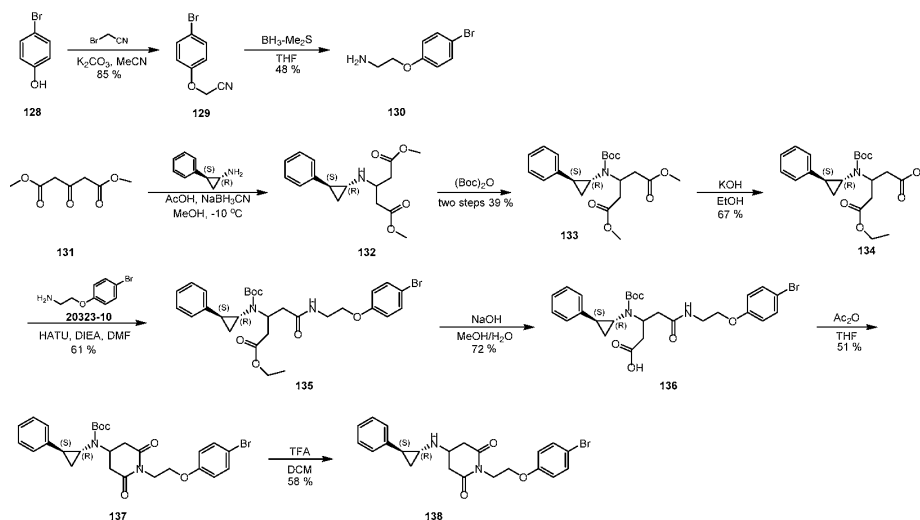
[0484] Compound **126**: To a mixture of 2-(4-oxo-1-piperidyl)-3-phenyl-propanoic acid (200 mg, 809 μmol , 1.00 *eq*) in DMF (8.00 mL) was added HATU (615 mg, 1.62 mmol, 2.00 *eq*) and DIPEA (209 mg, 1.62 mmol, 282 μL , 2.00 *eq*) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 hour, morpholine (141 mg, 1.62 mmol, 142 μL , 2.00 *eq*) was added, and the mixture was stirred at 0-15 °C for 11.5 hours. After completion, the reaction mixture was diluted with water (30 mL), then extracted with DCM (2 $\times$ 15 mL), the combined organic layer was washed with brine (2 $\times$ 40 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-TLC (Petroleum ether: Ethyl acetate=1:1) to give 1-(1-benzyl-2-morpholino-2-oxo-ethyl)piperidin-4-one (140 mg, 442 μmol , 54.7 % yield, 100 % purity) as yellow solid. LCMS $[\text{M}+1]$: 317.

[0485] ^1H NMR (400 MHz, Chloroform- d) δ 7.32 - 7.20 (m, 5H), 3.85 (dd, $J=4.0, 10.0$ Hz, 1H), 3.62 - 3.41 (m, 6H), 3.29 - 3.02 (m, 5H), 2.99 - 2.92 (m, 3H), 2.46 (t, $J=6.0$ Hz, 4H)

[0486] Compound **127**: To a mixture of 1-(1-benzyl-2-morpholino-2-oxo-ethyl)piperidin-4-one (140 mg, 442 μmol , 1.00 *eq*) in MeOH (10.0 mL) was added (1*R*,2*S*)-2-phenylcyclopropanamine (58.9 mg, 442 μmol , 1.00 *eq*) and AcOH (53.1 mg, 885 μmol , 50.6 μL , 2.00 *eq*) at -10 °C. The resulting mixture was stirred at -10 °C for 0.5 hour, NaBH_3CN (83.4 mg, 1.33 mmol, 3.00 *eq*) was added in portions, and the mixture was stirred at 0 - 15 °C for 11.5 hours. After completion, the reaction mixture was diluted with water (15 mL), then extracted with DCM (2 $\times$ 15 mL), the organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC (Instrument: GX-F; Column: Phenomenex Gemini 150*25mm*10 μm ; Condition: water (0.05 % HCl)-ACN; Begin B: 5; End B: 29; Gradient Time (min): 8; 100%B Hold Time (min): 2; FlowRate (ml/min): 25), the obtained product was concentrated and then lyophilized. The product 1-morpholino-3-phenyl-2-[4-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-1-piperidyl]propan-1-one (85.0 mg, 168 μmol , 37.9 % yield, 100 % purity, 2HCl) was obtained as a white solid. LCMS $[\text{M}+1]$: 434.

[0487] ^1H NMR (400 MHz, Deuterium oxide) δ 7.41 - 7.29 (m, 5H), 7.28 - 7.18 (m, 3H), 7.15 (d, $J=8.0$ Hz, 2H), 4.16 - 3.92 (m, 1H), 3.75 - 3.71 (m, 1H), 3.62 - 3.45 (m, 4H), 3.41 - 3.06 (m, 7H), 3.04 - 2.90 (m, 2H), 2.85 - 2.62 (m, 1H), 2.56 - 2.33 (m, 3H), 2.33 - 2.20 (m, 1H), 2.16 - 1.91 (m, 2H), 1.53 - 1.39 (m, 2H)

EXAMPLE 47

1-(2-(4-bromophenoxy)ethyl)-4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidine-2,6-dione

[0488] Compound 138, Example 47, was prepared from compound 128.

[0489] Compound 129: To a mixture of 4-bromophenol (2.00 g, 11.6 mmol, 1.00 *eq*) and 2-bromoacetonitrile (1.66 g, 13.9 mmol, 924 μ L, 1.20 *eq*) in MeCN (30.0 mL) was added K_2CO_3 (3.99 g, 28.9 mmol, 2.50 *eq*), and the mixture was stirred at 80 °C for 3 hours. After completion, solids were removed by filtration and the filtrate concentrated. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=1/0 to 10:1) to give 2-(4-bromophenoxy)acetonitrile (2.10 g, 9.83 mmol, 85.1 % yield, 99.3 % purity) as white solid.

[0490] 1H NMR (400 MHz, Chloroform-*d*) δ 7.49 (d, $J=9.2$ Hz, 2H), 6.90 (d, $J=9.2$ Hz, 2H), 4.77 (s, 2H).

[0491] Compound 130: To a mixture of 2-(4-bromophenoxy)acetonitrile (1.90 g, 8.96 mmol, 1.00 *eq*) in THF (20.0 mL) was added $BH_3 \cdot THF$ (1 M, 26.9 mL, 3.00 *eq*) in portions at 0 °C, the reaction was stirred at 0 °C for 2 hours, then the reaction mixture was heated to 80 °C and stirred at 80 °C for 12 hours. After completion, the reaction mixture was quenched with MeOH (30 mL) until no gas was formed, then concentrated. The residue was purified by column chromatography (SiO_2 , Petroleum ether:Ethyl acetate=5:1 to Dichloromethane: Methanol=10:1) to give 2-(4-bromophenoxy)ethanamine (1.60 g, 7.26 mmol, 80.9 % yield, 97.9 % purity) as yellow oil. LCMS [$M+1$, $M+3$]: 216, 218.

[0492] Compound 132: To a mixture of dimethyl 3-oxopentanedioate (686 mg, 3.94 mmol, 567 μ L, 1.05 *eq*) and (1*R*,2*S*)-2-phenylcyclopropanamine (500 mg, 3.75 mmol, 1.00 *eq*) in MeOH (15.0 mL) was added AcOH (450 mg, 7.50 mmol, 429 μ L, 2.00 *eq*) at -10 °C. The

mixture was stirred at -10 °C for 1 hour, then NaBH₃CN (707 mg, 11.3 mmol, 3.00 *eq*) was added to the mixture in portions at -10 °C, and the reaction was stirred at -10 ~ 0 °C for 2 hours. After completion, the reaction mixture was added to water (20 mL), then extracted with DCM (2 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give dimethyl 3-[[*(1R,2S)*-2-phenylcyclopropyl]amino]pentanedioate (1.00 g, crude) as yellow oil. LCMS [M+1]: 292.

[0493] Compound **133**: A mixture of dimethyl 3-[[*(1R,2S)*-2-phenylcyclopropyl]amino]pentanedioate (900 mg, 3.09 mmol, 1.00 *eq*) in (Boc)₂O (9.50 g, 43.5 mmol, 10.0 mL, 14.1 *eq*) was stirred at 15 °C for 12 hours. After completion, the mixture was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 5/1) to give dimethyl 3-*tert*-butoxycarbonyl-[[*(1R,2S)*-2-phenylcyclopropyl] amino]pentanedioate (500 mg, 1.20 mmol, 38.7 % yield, 93.7 % purity) as a colorless oil. LCMS [M-99]: 292

[0494] ¹H NMR (400 MHz, Chloroform-*d*) δ 7.31 - 7.25 (m, 2H), 7.22 - 7.08 (m, 3H), 4.38 - 4.29 (m, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.10 - 2.93 (m, 2H), 2.77 - 2.63 (m, 3H), 2.18 - 2.14 (m, 1H), 1.48 - 1.35 (m, 10H), 1.31 - 1.14 (m, 1H).

[0495] Compound **134**: To a mixture of dimethyl 3-*tert*-butoxycarbonyl-[[*(1R,2S)*-2-phenylcyclopropyl]amino]pentanedioate (400 mg, 1.02 mmol, 1.00 *eq*) in EtOH (15.0 mL) was added KOH (80.8 mg, 1.22 mmol, 85 % purity, 1.20 *eq*), and the reaction was stirred at 15 °C for 4 hours. After completion, the reaction mixture was adjusted with 1 M HCl to pH ~6, then extracted with DCM (2 × 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give 3-*tert*-butoxycarbonyl-[[*(1R,2S)*-2-phenylcyclopropyl]amino]-5-ethoxy-5-oxo-pentanoic acid (270 mg, 684 umol, 67.1 % yield, 99.2 % purity) as yellow oil. LCMS [M-99]: 292.

[0496] Compound **135**: To a mixture of 3-*tert*-butoxycarbonyl-[[*(1R,2S)*-2-phenylcyclopropyl]amino]-5-ethoxy-5-oxo-pentanoic acid (330 mg, 843 umol, 1.00 *eq*) in DMF (10.0 mL) was added HATU (641 mg, 1.69 mmol, 2.00 *eq*) and DIPEA (218 mg, 1.69 mmol, 294 uL, 2.00 *eq*) at 0 °C. After the reaction was stirred at 0 °C for 0.5 hour, 2-(4-bromophenoxy)ethanamine (237 mg, 1.10 mmol, 1.30 *eq*) was added, and the mixture was stirred at 0 - 15 °C for 11.5 hours. After completion, the reaction mixture was added to water (15 mL), then extracted with DCM (2 × 15 mL), the combined organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate=50:1~3:1) to give ethyl 5-[2-(4-bromophenoxy)ethylamino]-3-*tert*-butoxycarbonyl-[[*(1R,2S)*- 2-phenylcyclopropyl]amino]-5-oxo-pentanoate (330 mg, 515 umol, 61.1 % yield, 92 % purity) as a yellow oil. LCMS [M-99]: 489,491.

[0497] Compound **136**: To a mixture of ethyl 5-[2-(4-bromophenoxy)ethylamino]-3-[*tert*-butoxycarbonyl-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-5-oxo-pentanoate (250 mg, 424 μ mol, 1.00 *eq*) in MeOH (2.00 mL) and H₂O (500 μ L) was added NaOH (67.9 mg, 1.70 mmol, 4.00 *eq*), and the mixture was stirred at 15 °C for 3 hours. After completion, the reaction mixture was diluted with 0.5 M HCl aqueous solution to pH~7, then the mixture was added to water (10 mL), and extracted with DCM (2 $\times$ 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give 5-[2-(4-bromophenoxy)ethylamino]-3-[*tert*-butoxycarbonyl-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-5-oxo-pentanoic acid (180 mg, 306 μ mol, 72.1 % yield, 95.4 % purity) as yellow solid. LCMS [M-99, M+23]: 463, 585.

[0498] Compound **137**: To a mixture of 5-[2-(4-bromophenoxy)ethylamino]-3-[*tert*-butoxycarbonyl-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]-5-oxo-pentanoic acid (120 mg, 214 μ mol, 1.00 *eq*) in THF (4.00 mL) was added Ac₂O (43.6 mg, 427 μ mol, 40.0 μ L, 2.00 *eq*), and the reaction was stirred at 70 °C for 12 hours under N₂. After completion, the reaction mixture was concentrated. The residue was purified by prep-TLC (Petroleum ether: Ethyl acetate=3:1) to give *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-2,6-dioxo-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (60.0 mg, 109 μ mol, 51.4 % yield, 99.5 % purity) as a white solid. LCMS [M-55, M+23]: 487, 567.

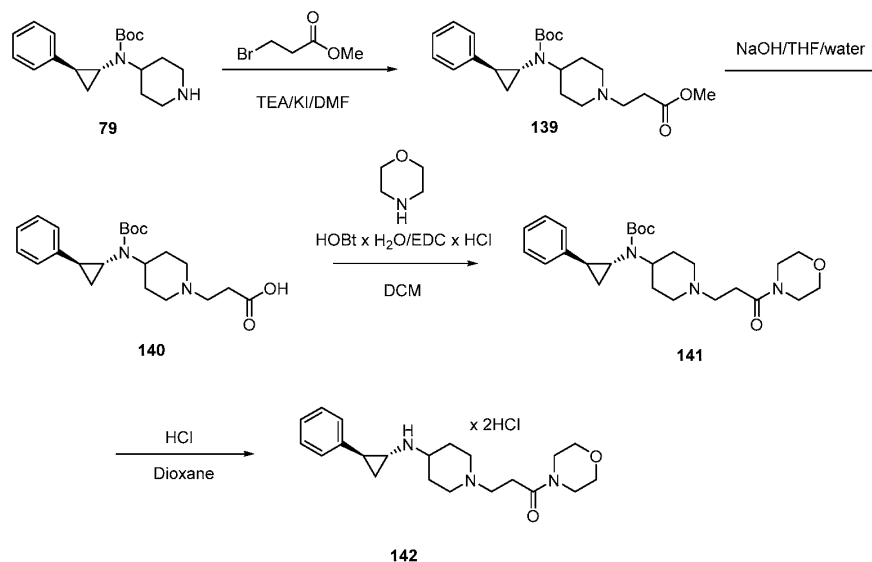
[0499] ¹H NMR (400 MHz, Chloroform-*d*) δ 7.40 - 7.19 (m, 5H), 7.11 - 7.04 (m, 2H), 6.81 - 6.74 (m, 2H), 4.18 (t, *J*=6.2 Hz, 2H), 4.13 - 4.03 (m, 3H), 3.45 - 3.30 (m, 2H), 2.93 - 2.82 (m, 2H), 2.74 - 2.67 (m, 1H), 2.19 - 2.06 (m, 1H), 1.42 (s, 9H), 1.33 - 1.25 (m, 2H).

[0500] Compound **138**: To a mixture of *tert*-butyl *N*-[1-[2-(4-bromophenoxy)ethyl]-2,6-dioxo-4-piperidyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]carbamate (60.0 mg, 110 μ mol, 1.00 *eq*) in DCM (500 μ L) was added TFA (770 mg, 6.75 mmol, 500 μ L, 61.2 *eq*), and the reaction was stirred at 15 °C for 1 hour. After completion, the reaction mixture was concentrated. The residue was purified by prep-HPLC ((Instrument: GX-E; Column: Phenomenex Synergi C18 150*25*10 μ m; Condition: water (0.05 % HCl)-ACN; Begin B: 35; End B: 55; Gradient Time (min): 7.8; 100%B Hold Time (min): 2; FlowRate (ml/min): 28). The obtained product was concentrated and then lyophilized. The product 1-[2-(4-bromophenoxy)ethyl]-4-[(1*R*,2*S*)-2-phenylcyclopropyl]amino]piperidine-2,6-dione (30.8 mg, 63.9 μ mol, 57.9 % yield, 99.8 % purity, HCl) was obtained as a yellow oil. LCMS [M+1]: 443, 445.

[0501] ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.41 - 7.31 (m, 4H), 7.29 - 7.17 (m, 3H), 6.85 (d, *J*=8.4 Hz, 2H), 4.20 - 4.06 (m, 5H), 3.32 - 3.22 (m, 2H), 3.18 - 3.01 (m, 3H), 2.65 - 2.54 (m, 1H), 1.68 - 1.56 (m, 1H), 1.53 - 1.43 (m, 1H).

EXAMPLE 48

1-Morpholino-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one dihydrochloride (**142**)



Step 1. Methyl 3-(4-(((*tert*-butoxycarbonyl)((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanoate (**139**)

[0502] To a solution of the intermediate **79** (1.00 g, 3.16 mmol) in DMF (8 mL) were added TEA (1.189 mL, 8.53 mmol), KI (131 mg, 0.790 mmol) and methyl-3-bromopropionate (0.345 mL, 3.16 mmol). The reaction mixture was stirred at RT for 4 hrs, diluted with brine and extracted with EA. The extract was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was subjected to flash column chromatography, eluent EA-hexanes (4:1) to afford title compound **65** (1.027 g, 81% yield) as a gum. The product contains 0.18 M of EA per 1M of the desired compound.

[0503] ¹H NMR: 500 MHz, acetone-d₆, δ (ppm): 7.32-7.28 (m, 2H), 7.21-7.18 (m, 3H), 3.68-3.62 (m, 1H), 3.65 (s, 3H), 3.00-2.93 (m, 2H), 2.65-2.61 (m, 3H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.19-2.10 (m, 3H), 2.06-2.00 (m, 2H), 1.76-1.67 (m, 2H), 1.43 (s, 9H), 1.42-1.38 (m, 1H), 1.29-1.25 (m, 1H). MS: 402.5 (calcd.), 403.3 (M+H⁺, found).

Step 2. 3-(4-(((*tert*-Butoxycarbonyl)((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanoic acid (**140**)

[0504] To a solution of ester **139** (1.027 g, 2.55 mmol) in THF (20 mL) was added a solution of NaOH (153 mg, 3.83 mmol) in water (10 mL). The reaction mixture was stirred at rt for 2 hrs. acidified to pH 5 with HCl. The acidic solution was evaporated in vacuum to form a glassy solid.

The material was then suspended in DCM, treated with hexanes and evaporated to afford the title compound **140** (1.13 g, 99% yield) as white fluffy solid which contained 1.5 eq of NaCl. The material was taken to the next step as is. MS: 388.5 (calcd.), 389.7 (M+H⁺, found).

Step 3. *tert*-Butyl (1-(3-morpholino-3-oxopropyl)piperidin-4-yl)((1*R*,2*S*)-2-phenylcyclopropyl)carbamate (**141**)

[0505] To a suspension of acid **140** (800 mg, 1.79 mmol) in DCM (30 mL) was added HOBt hydrate (548 mg, 3.58 mmol), EDC hydrochloride (1.029 g, 5.37 mmol) and morpholine (0.627 mL, 7.16 mmol). The reaction mixture was stirred overnight at rt, diluted with more DCM and washed with brine. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography, eluent 5 then 10% MeOH (with 2% ammonia) in DCM to afford title compound **141** (748 mg, 91% yield) as a honey-like material that contains ca 0.6 M of DCM per 1M of the product. The material was taken to the next step as is.

[0506] ¹H NMR: 500 MHz, CD₃OD, δ (ppm): 7.26-7.23 (m, 2H), 7.16-7.10 (m, 3H), 3.72-3.68 (m, 1H), 3.67-3.62 (m, 4H), 3.57-3.53 (m, 4H), 3.05-2.98 (m, 2H), 2.69-2.66 (m, 2H), 2.62-2.56 (m, 3H), 2.13-2.09 (m, 4H), 2.02-1.94 (m, 1H), 1.82-1.79 (m, 1H), 1.75-1.72 (m, 1H), 1.41 (s, 9H), 1.40-1.38 (m, 1H), 1.25-1.21 (m, 1H). MS: 457.6 (calcd.), 458.4 (M+H⁺, found).

Step 4. 1-Morpholino-3-(4-(((1*R*,2*S*)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one di-hydrochloride (**142**)

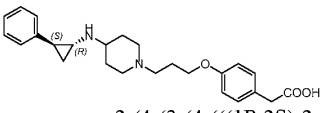
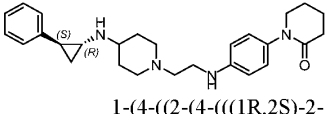
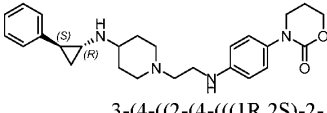
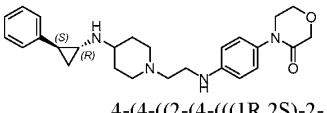
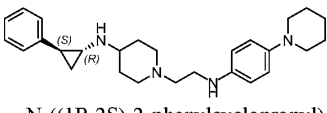
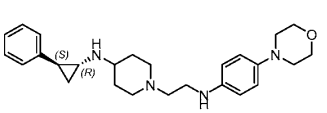
[0507] To a solution of compound **141** (748 mg, 1.635 mmol) in dioxane (7.0 mL) at rt was added a 4M HCl solution of in dioxane (12.0 mL, 48 mmol). The mixture was stirred at ambient temperature for 3 hrs, evaporated to dryness in vacuum. The resultant white precipitate was triturated with acetone to afford title compound **142** (637 mg, 91% yield) as a white solid (Example 48).

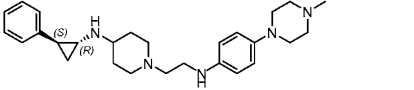
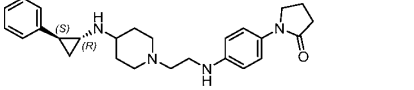
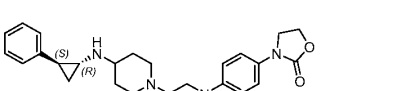
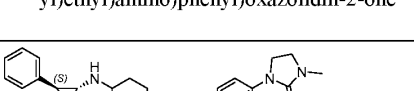
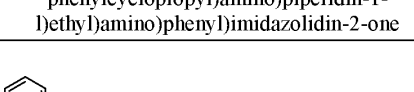
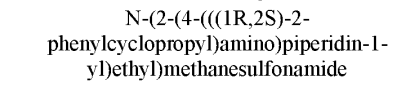
[0508] ¹H NMR: 500 MHz, DMSO-*d*₆, δ (ppm): 10.71 and 10.52 (two bs, 1H, mixture of rotamers), 10.18 and 10.02 (2 bs, 2H, mixture of rotamers), 7.32-7.29 (m, 2H), 7.24-7.17 (m, 3H), 3.61-3.59 (m, 4H), 3.56-3.54 (m, 2H), 3.45-3.44 (m, 5H), 3.24 (bt, 2H), 3.03-2.94 (m, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.68-2.65 and 2.59-2.55 (two m, 1H, mixture of rotamers), 2.32-2.21 (bs, 2H), 2.11-2.01 (m, 2H), 1.66 and 1.60-1.56 (bs and m, 1H, mixture of rotamers), 1.31-1.27 (m, 1H). MS: 357.5 (calcd.), 358.7 (M+H⁺, found).

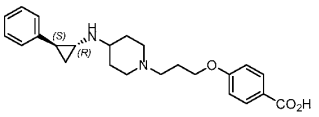
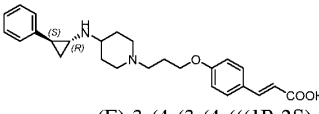
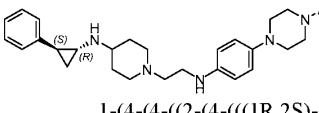
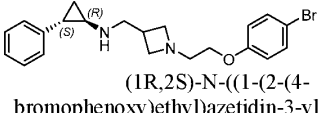
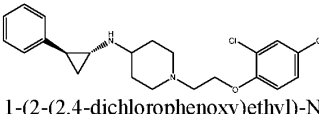
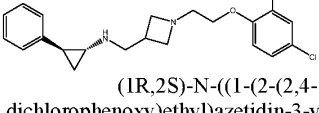
[0509] Following the general teachings of the Reaction Schemes and specific synthetic routes set forth herein, the additional following compounds were prepared:

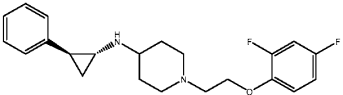
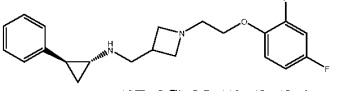
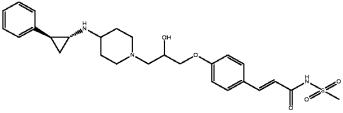
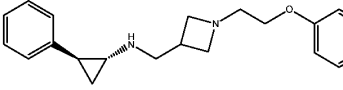
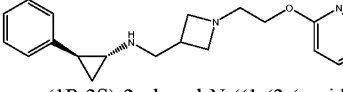
Table 2

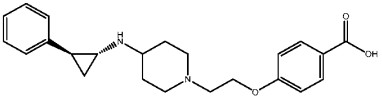
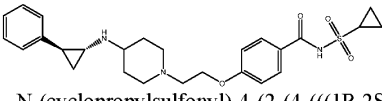
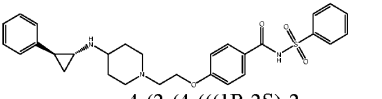
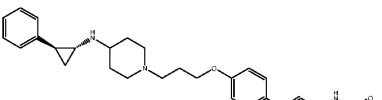
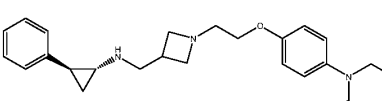
Further Exemplary Compounds of Formula (I) and Formula (II)

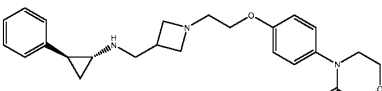
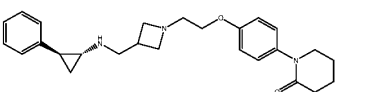
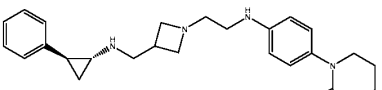
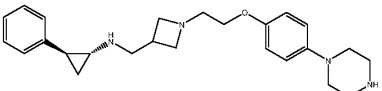
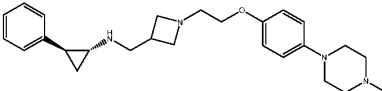
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
49	 2-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acetic acid	Scheme 2b	409.4	(400 MHz, methanol-d ₄) δ 7.38 - 7.30 (m, 2H), 7.29 - 7.18 (m, 5H), 6.91 (d, <i>J</i> = 8.8 Hz, 2H), 4.13 (t, <i>J</i> = 5.4 Hz, 2H), 3.89 - 3.68 (m, 3H), 3.60 - 3.52 (m, 2H), 3.40 - 3.31 (m, 2H), 3.26 - 3.12 (m, 2H), 3.07 - 3.04 (m, 1H), 2.67 - 2.42 (m, 3H), 2.34 - 2.09 (m, 4H), 1.65 - 1.56 (m, 1H), 1.52 - 1.46 (m, 1H).
50	 1-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)piperidin-2-one	Example 20	433.3	(400 MHz, deuterium oxide) δ 7.28 - 7.21 (m, 2H), 7.20 - 7.14 (m, 3H), 7.13 - 7.03 (m, 4H), 3.70 - 3.57 (m, 5H), 3.50 - 3.47 (m, 2H), 3.40 - 3.36 (m, 2H), 3.19 - 3.02 (m, 2H), 2.89 - 2.85 (m, 1H), 2.45 - 2.28 (m, 5H), 2.00 - 1.72 (m, 6H), 1.45 - 1.29 (m, 2H)
51	 3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one	Example 20	435.4	(400 MHz, deuterium oxide) δ 7.32 - 7.17 (m, 5H), 7.10 (d, <i>J</i> = 7.6 Hz, 2H), 7.03 (d, <i>J</i> = 8.8 Hz, 2H), 4.35 (t, <i>J</i> = 5.2 Hz, 2H), 3.74 - 3.54 (m, 7H), 3.44 - 3.34 (m, 2H), 3.13 - 3.04 (m, 2H), 2.93 - 2.86 (m, 1H), 2.48 - 2.31 (m, 3H), 2.15 - 1.85 (m, 4H), 1.50 - 1.32 (m, 2H)
52	 4-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)morpholin-3-one	Example 20	435.2	(400 MHz, deuterium oxide) δ 7.38 - 7.04 (m, 7H), 7.00 - 6.76 (m, 2H), 4.24 (s, 2H), 4.05 - 3.91 (m, 2H), 3.74 - 3.51 (m, 7H), 3.42 - 3.28 (m, 2H), 3.20 - 3.09 (m, 2H), 2.94 - 2.86 (m, 1H), 2.51 - 2.25 (m, 3H), 2.02 - 1.84 (m, 2H), 1.51 - 1.30 (m, 2H)
53	 N-((1R,2S)-2-phenylcyclopropyl)-1-(2-((4-(piperidin-1-yl)phenyl)amino)ethyl)piperidin-4-amine	Example 20	419.3	(400 MHz, deuterium oxide) δ 7.36 - 7.26 (m, 4H), 7.25 - 7.17 (m, 1H), 7.12 - 7.10 (m, 2H), 6.78 - 6.75 (m, 2H), 3.79 - 3.58 (m, 3H), 3.57 - 3.39 (m, 6H), 3.35 - 3.26 (m, 2H), 3.20 - 2.99 (m, 2H), 2.93 - 2.91 (m, 1H), 2.54 - 2.29 (m, 3H), 2.06 - 1.70 (m, 7H), 1.60 - 1.32 (m, 3H)
54	 1-(2-((4-morpholinophenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 20	421.2	(400 MHz, deuterium oxide) δ 7.33 (d, <i>J</i> = 8.8 Hz, 2H), 7.28 - 7.12 (m, 3H), 7.08 - 7.02 (m, 2H), 6.77 (d, <i>J</i> = 8.0 Hz, 2H), 4.02 - 3.92 (m, 4H), 3.72 - 3.45 (m, 9H), 3.29 - 3.24 (m, 2H), 3.12 - 3.06 (m, 2H), 2.94 - 2.82 (m, 1H), 2.48 - 2.23 (m, 3H), 2.04 - 1.85 (m, 2H), 1.49 - 1.28 (m, 2H)

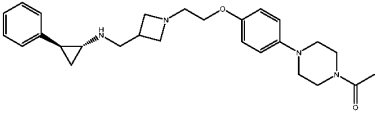
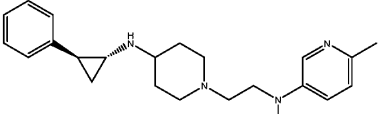
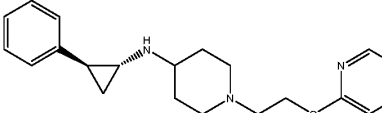
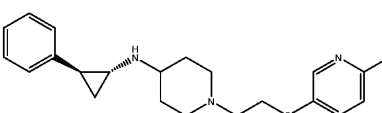
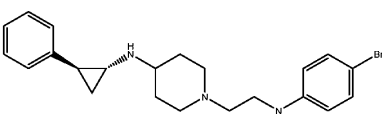
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
55	 1-(2-((4-(4-methylpiperazin-1-yl)phenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 20	434.3	(400 MHz, deuterium oxide) δ 7.40 - 6.99 (m, 9H), 3.95 - 3.54 (m, 9H), 3.51 - 3.05 (m, 8H), 3.00 - 2.86 (m, 4H), 2.51 - 2.29 (m, 3H), 2.05 - 1.88 (m, 2H), 1.52 - 1.33 (m, 2H)
56	 1-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)pyrrolidin-2-one	Example 20	419.3	(400 MHz, deuterium oxide) δ 7.42 (d, J = 8.4 Hz, 2H), 7.29 - 7.10 (m, 5H), 7.09 - 6.99 (m, 2H), 3.83 - 3.54 (m, 7H), 3.42 - 3.38 (m, 2H), 3.14 - 3.08 (m, 2H), 2.89 - 2.72 (m, 1H), 2.53 - 2.27 (m, 5H), 2.08 - 1.82 (m, 4H), 1.45 - 1.26 (m, 2H)
57	 3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)oxazolidin-2-one	Example 20	421.2	(400 MHz, deuterium oxide) δ 7.36 (d, J = 8.8 Hz, 2H), 7.29 - 7.23 (m, 2H), 7.22 - 7.16 (m, 1H), 7.08 - 7.03 (m, 4H), 4.40 (t, J = 8.2 Hz, 2H), 3.98 (t, J = 8.2 Hz, 2H), 3.71 - 3.57 (m, 5H), 3.42 - 3.33 (m, 2H), 3.16 - 3.04 (m, 2H), 2.90 - 2.88 (m, 1H), 2.47 - 2.29 (m, 3H), 2.02 - 1.85 (m, 2H), 1.50 - 1.31 (m, 2H).
58	 1-methyl-3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)imidazolidin-2-one	Example 20	434.2	(400 MHz, deuterium oxide) δ 7.57 - 7.33 (m, 2H), 7.33 - 7.04 (m, 7H), 3.91 - 3.55 (m, 7H), 3.52 - 3.34 (m, 4H), 3.21 - 3.06 (m, 2H), 2.92 - 2.90 (m, 4H), 2.48 - 2.32 (m, 3H), 2.05 - 1.85 (m, 2H), 1.50 - 1.33 (m, 2H).
59	 N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)methanesulfonamide	Scheme 3b	338.1	(400 MHz, methanol- d_4) δ 7.37 - 7.31 (m, 2H), 7.29 - 7.24 (m, 1H), 7.22 (d, J = 7.6 Hz, 2H), 3.86 (d, J = 12.0 Hz, 2H), 3.79 - 3.64 (m, 1H), 3.61 - 3.47 (m, 2H), 3.39 - 3.34 (m, 2H), 3.28 - 3.15 (m, 2H), 3.10 - 3.00 (m, 4H), 2.60 - 2.54 (m, 1H), 2.48 (t, J = 12.4 Hz, 2H), 2.20 - 2.05 (m, 2H), 1.65 - 1.56 (m, 1H), 1.50 - 1.43 (m, 1H)
60	 N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)benzenesulfonamide	Scheme 3b	400.2	(400 MHz, methanol- d_4) δ 7.93 (d, J = 7.2 Hz, 2H), 7.73 - 7.67 (m, 1H), 7.67 - 7.60 (m, 2H), 7.39 - 7.30 (m, 2H), 7.30 - 7.24 (m, 1H), 7.22 (d, J = 7.6 Hz, 2H), 3.84 (d, J = 12.8 Hz, 2H), 3.77 - 3.67 (m, 1H), 3.50 (br. s., 1H), 3.30 - 3.18 (m, 4H), 3.09 - 3.04 (m, 1H), 2.62 - 2.55 (m, 1H), 2.49 (t, J = 12.8 Hz, 2H), 2.35 (br. s., 1H), 2.23 - 2.13 (m, 2H), 1.73 - 1.58 (m, 1H), 1.50 - 1.42 (q, J = 7.1 Hz, 1H).

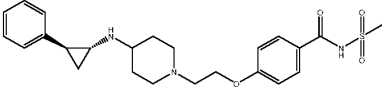
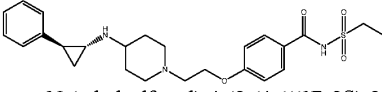
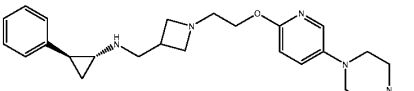
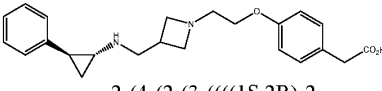
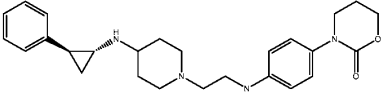
Ex. #	Structure	Method	LCMS [M+] Observed	¹ H NMR
61	 4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)benzoic acid	Scheme 2b	395.2	(400 MHz, DMSO-d ₆) δ 10.55 (s, 1H), 10.24 - 9.59 (m, 3H), 7.91 (d, <i>J</i> = 8.4 Hz, 2H), 7.37 - 7.28 (m, 2H), 7.27 - 7.16 (m, 3H), 7.03 (d, <i>J</i> = 8.8 Hz, 2H), 4.14 (t, <i>J</i> = 5.8 Hz, 2H), 3.65 - 3.53 (m, 2H), 3.54 - 3.46 (m, 1H), 3.21 - 3.09 (m, 2H), 3.07 - 2.92 (m, 3H), 2.39 - 1.95 (m, 7H), 1.63 - 1.52 (m, 1H), 1.33 - 1.29 (m, 1H).
62	 (E)-3-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylic acid	Example 34	421.2	(400 MHz, DMSO-d ₆) δ 12.27 (br. s., 1H), 10.59 (br. s., 1H), 9.98 (br. s., 2H), 7.65 (d, <i>J</i> = 8.4 Hz, 2H), 7.55 (d, <i>J</i> = 16.0 Hz, 1H), 7.40 - 7.28 (m, 2H), 7.27 - 7.15 (m, 3H), 6.98 (d, <i>J</i> = 8.0 Hz, 2H), 6.39 (d, <i>J</i> = 16.0 Hz, 1H), 4.11 (t, <i>J</i> = 5.6 Hz, 2H), 3.66 - 3.55 (m, 2H), 3.20 - 3.08 (m, 3H), 3.02 - 2.96 (m, 3H), 2.41 - 1.95 (m, 7H), 1.64 - 1.53 (m, 1H), 1.36 - 1.25 (m, 1H).
63	 1-(4-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)piperazin-1-yl)ethan-1-one	Example 20	462.2	(400 MHz, deuterium oxide) δ 7.28 (d, <i>J</i> = 8.8 Hz, 2H), 7.19 - 7.10 (m, 3H), 7.05 - 6.96 (m, 2H), 6.78 - 6.75 (m, 2H), 3.88 - 3.73 (m, 4H), 3.68 - 3.51 (m, 5H), 3.39 - 3.36 (m, 4H), 3.27 - 3.22 (m, 2H), 3.04 - 2.98 (m, 2H), 2.84 - 2.80 (m, 1H), 2.42 - 2.22 (m, 3H), 2.01 (s, 3H), 1.98 - 1.82 (m, 2H), 1.43 - 1.22 (m, 2H).
64	 (1R,2S)-N-((1-(2-(4-bromophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine	Example 12	403.1	(400 MHz, Methanol-d ₄) δ 7.46 (d, <i>J</i> = 9.2 Hz, 2H), 7.38 - 7.29 (m, 2H), 7.29 - 7.18 (m, 3H), 6.96 (d, <i>J</i> = 9.2 Hz, 2H), 4.50 - 4.41 (m, 2H), 4.36 - 4.20 (m, 4H), 3.82 - 3.57 (m, 4H), 3.48 - 3.37 (m, 1H), 3.07 - 2.96 (m, 1H), 2.64 - 2.58 (m, 1H), 1.64 - 1.59 (m, 1H), 1.46 - 1.41 (m, 1H).
65	 1-(2-(2,4-dichlorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Scheme 2b	405.1	(400 MHz, Methanol-d ₄) δ 7.50 (d, <i>J</i> = 2.8 Hz, 1H), 7.39 - 7.31 (m, 3H), 7.30 - 7.16 (m, 4H), 4.61 - 4.50 (m, 2H), 4.01 - 3.95 (m, 2H), 3.84 - 3.66 (m, 3H), 3.42 - 3.36 (m, 2H), 3.08 - 3.04 (m, 1H), 2.63 - 2.40 (m, 3H), 2.24 - 2.18 (m, 2H), 1.71 - 1.57 (m, 1H), 1.52 - 1.46 (m, 1H).
66	 (1R,2S)-N-((1-(2-(2,4-dichlorophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine	Example 11	391.0	(400 MHz, deuterium oxide) δ 7.49 (d, <i>J</i> = 2.8 Hz, 1H), 7.39 - 7.29 (m, 3H), 7.29 - 7.18 (m, 3H), 7.15 (d, <i>J</i> = 8.8 Hz, 1H), 4.61 - 4.48 (m, 2H), 4.42 - 4.26 (m, 4H), 3.83 - 3.76 (m, 2H), 3.73 - 3.60 (m, 2H), 3.43 - 3.34 (m, 1H), 3.06 - 2.98 (m, 1H), 2.62 - 2.55 (m, 1H), 1.64 - 1.56 (m, 1H), 1.47 - 1.41 (m, 1H).

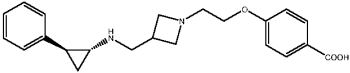
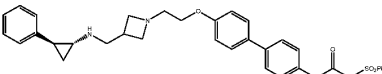
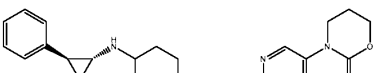
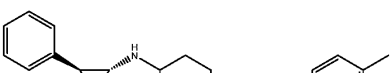
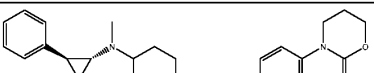
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
67	 1-(2-(2,4-difluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Scheme 2b	373.2	(400 MHz, deuterium oxide) δ 7.31 - 7.23 (m, 2H), 7.22 - 7.16 (m, 1H), 7.09 (d, J = 7.2 Hz, 2H), 7.04 - 7.00 (m, 1H), 6.95 - 6.91 (m, 1H), 6.86 - 6.77 (m, 1H), 4.37 - 4.26 (m, 2H), 3.83 - 3.59 (m, 3H), 3.57 - 3.48 (m, 2H), 3.21 - 3.13 (m, 2H), 2.94 - 2.87 (m, 1H), 2.49 - 2.30 (m, 3H), 2.06 - 1.88 (m, 2H), 1.50 - 1.33 (m, 2H)
68	 (1R,2S)-N-((1-(2-(2,4-difluorophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine	Example 11	359.2	(400 MHz, deuterium oxide) δ 7.26 - 7.19 (m, 2H), 7.17 - 7.11 (m, 1H), 7.07 (d, J = 7.2 Hz, 2H), 7.02 - 6.88 (m, 2H), 6.85 - 6.77 (m, 1H), 4.42 - 4.28 (m, 2H), 4.21 - 3.98 (m, 4H), 3.68 - 3.42 (m, 4H), 3.39 - 3.25 (m, 1H), 2.94 - 2.83 (m, 1H), 2.44 - 2.38 (m, 1H), 1.47 - 1.38 (m, 1H), 1.36 - 1.28 (m, 1H).
69	 (E)-3-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)-N-(methylsulfonyl)acrylamide	Example 35	514.3	(400 MHz, deuterium oxide) δ 7.57 (d, J = 15.6 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.34 - 7.19 (m, 3H), 7.12 (d, J = 7.6 Hz, 2H), 6.98 - 6.88 (m, 2H), 6.29 (d, J = 16 Hz, 1H), 4.49 - 4.42 (m, 1H), 4.12 - 3.98 (m, 2H), 3.84 - 3.61 (m, 3H), 3.43 - 3.25 (m, 5H), 3.24 - 3.00 (m, 2H), 2.94 - 2.92 (m, 1H), 2.51 - 2.31 (m, 3H), 2.12 - 1.92 (m, 2H), 1.53 - 1.36 (m, 2H).
70	 (1R,2S)-2-phenyl-N-((1-(2-(p-tolyl)oxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine	Example 10	337.2	(400 MHz, METHANOL- d_4) δ = 7.31 - 7.29 (d, J = 7.6 Hz, 2H), 7.25 - 7.18 (m, 3H), 7.12 - 7.10 (d, J = 8.4 Hz, 2H), 6.88 - 6.85 (d, J = 8.4 Hz, 2H), 4.50 - 4.38 (m, 2H), 4.20 (m, 4H), 3.69 (m, 4H), 3.40 (br s, 1H), 3.01 (br s, 1H), 2.61 - 2.56 (m, 1H), 2.27 (s, 3H), 1.60 - 1.57 (m, 1H), 1.43 - 1.39 (q, J = 6.8 Hz, 1H)
71	 (1R,2S)-2-phenyl-N-((1-(2-(pyridin-2-yloxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine	Example 10	324.2	(400 MHz, METHANOL- d_4) δ = 8.36 - 8.35 (br d, J = 5.2 Hz, 1H), 8.25 (br s, 1H), 7.40 - 7.38 (br d, J = 6.4 Hz, 2H), 7.31 - 7.29 (m, 2H), 7.24 - 7.19 (m, 3H), 4.70 (br s, 2H), 4.50 - 4.47 (m, 2H), 4.32 - 4.30 (m, 2H), 3.84 (br s, 2H), 3.73 (br s, 1H), 3.61 - 3.59 (br d, J = 5.2 Hz, 1H), 3.41 (br s, 1H), 3.02 (br s, 1H), 2.64 - 2.59 (m, 1H), 1.65 - 1.59 (m, 1H), 1.41 - 1.39 (m, 1H)

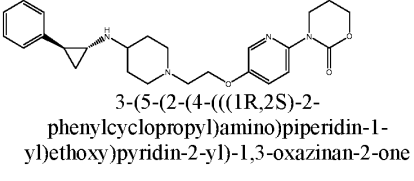
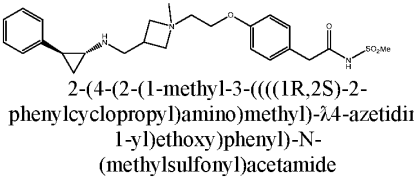
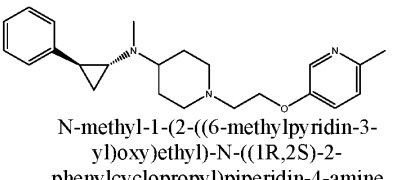
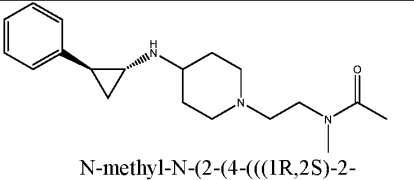
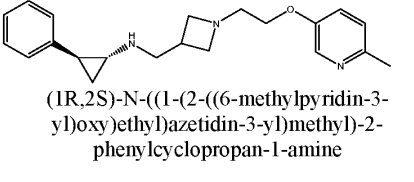
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
72	 4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)pipe-ridin-1-yl)ethoxy)benzoic acid	Example 15	381.1	(400 MHz, Deuterium oxide) δ 7.89 - 7.81 (m, 2H), 7.32 - 7.18 (m, 3H), 7.10 (d, <i>J</i> =7.2 Hz, 2H), 6.99 - 6.91 (m, 2H), 4.43 - 4.29 (m, 2H), 3.82 - 3.60 (m, 3H), 3.58 - 3.52 (m, 2H), 3.34 - 3.08 (m, 2H), 2.94 - 2.89 (m, 1H), 2.50 - 2.31 (m, 3H), 2.06 - 1.89 (m, 2H), 1.50 - 1.34 (m, 2H)
73	 N-(cyclopropylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)pipe-ridin-1-yl)ethoxy)benzamide	Example 16	484.2	¹ H NMR: 500 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 11.93 (bs, 1H), 10.93 (bs, 1H), 10.01 (bs, 2H), 7.96 (d, <i>J</i> = 9.0 Hz, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 7.12 (d, <i>J</i> = 9.0 Hz, 2H), 4.50 (bt, 2H), 3.69-3.67 (m, 2H), 3.50-3.49 (m, 4H), 3.18-3.10 (m, 3H), 2.97 (bs, 1H), 2.57 (bs, 1H), 2.31 (bs, 2H), 2.12 (bs, 1H), 1.59 (bs, 1H), 1.31-1.29 (m, 1H), 1.17-1.08 (m, 4H).
74	 4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)pipe-ridin-1-yl)ethoxy)-N-(phenylsulfonyl)benzamide	Example 16	520.2	¹ H NMR: 500 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 12.40 (bs, 1H), 10.88 (bs, 1H), 9.99 (bs, 2H), 8.00-7.99 (m, 2H), 7.89 (d, <i>J</i> = 9.0 Hz, 2H), 7.73-7.70 (m, 1H), 7.66-7.62 (m, 2H), 7.32-7.29 (m, 2H), 7.24-7.17 (m, 3H), 7.08 (d, <i>J</i> = 9.0 Hz, 2H), 4.48 (bt, 2H), 3.68-3.65 (m, 2H), 3.48 (bs, 4H), 3.13 (bs, 2H), 2.97 (bs, 1H), 2.57 (bs, 1H), 2.30 (bs, 2H), 2.10 (bs, 1H), 1.59 (bs, 1H), 1.31-1.28 (m, 1H).
75	 (E)-N-(methylsulfonyl)-3-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)pipe-ridin-1-yl)propoxy)phenyl)acrylamide	Example 16	498.3	(400 MHz, deuterium oxide) □ 7.53 - 7.45 (m, 3H), 7.32 - 7.24 (m, 2H), 7.24 - 7.18 (m, 1H), 7.10 (d, <i>J</i> = 7.2 Hz, 2H), 6.87 (d, <i>J</i> = 8.8 Hz, 2H), 6.20 (d, <i>J</i> = 16.0 Hz, 1H), 4.07 (t, <i>J</i> = 5.4 Hz, 2H), 3.77 - 3.58 (m, 3H), 3.33 - 3.21 (m, 5H), 3.11 - 2.96 (m, 2H), 2.93 - 2.85 (m, 1H), 2.50 - 2.32 (m, 3H), 2.20 - 2.10 (m, 2H), 1.96 - 1.82 (m, 2H), 1.51 - 1.34 (m, 2H)
76	 3-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one	Examples 10 and 20	422.2	(400 MHz, deuterium oxide) □ 7.28 - 7.21 (m, 2H), 7.20 - 7.13 (m, 3H), 7.08 (d, <i>J</i> = 7.6 Hz, 2H), 6.93 - 6.85 (m, 2H), 4.38 - 4.25 (m, 4H), 4.20 - 3.99 (m, 4H), 3.66 - 3.50 (m, 5H), 3.48 - 3.44 (m, 1H), 3.39 - 3.26 (m, 1H), 2.92 - 2.81 (m, 1H), 2.47 - 2.38 (m, 1H), 2.10 - 2.05 (m, 2H), 1.49 - 1.38 (m, 1H), 1.36 - 1.25 (m, 1H).

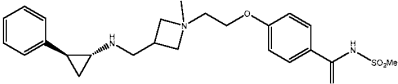
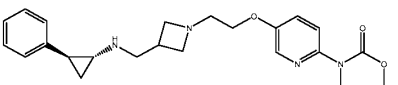
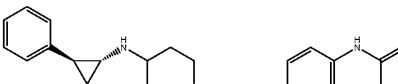
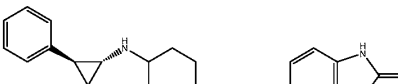
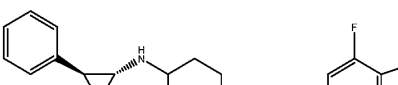
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
77	 4-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)morpholin-3-one	Examples 10 and 20	422.2	(400 MHz, deuterium oxide) δ 7.26 - 7.19 (m, 2H), 7.19 - 7.12 (m, 3H), 7.07 (d, J = 7.6 Hz, 2H), 6.95 - 6.87 (m, 2H), 4.36 - 4.25 (m, 2H), 4.23 - 4.20 (m, 2H), 4.19 - 4.07 (m, 3H), 4.06 - 3.99 (m, 1H), 3.95 (t, J = 5.0 Hz, 2H), 3.64 - 3.60 (m, 3H), 3.55 - 3.52 (m, 2H), 3.48 - 3.44 (m, 1H), 3.42 - 3.30 (m, 1H), 2.91 - 2.79 (m, 1H), 2.49 - 2.36 (m, 1H), 1.49 - 1.37 (m, 1H), 1.35 - 1.25 (m, 1H)
78	 1-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)piperidin-2-one	Examples 10 and 20	420.2	(400 MHz, deuterium oxide) δ 7.29 - 7.20 (m, 2H), 7.19 - 7.13 (m, 1H), 7.12 - 7.04 (m, 4H), 6.94 - 6.86 (m, 2H), 4.37 - 4.24 (m, 2H), 4.20 - 3.99 (m, 4H), 3.65 - 3.43 (m, 6H), 3.38 - 3.26 (m, 1H), 2.92 - 2.81 (m, 1H), 2.47 - 2.33 (m, 3H), 1.86 - 1.73 (m, 4H), 1.48 - 1.38 (m, 1H), 1.37 - 1.27 (m, 1H)
79	 3-(4-((2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one	Examples 10 and 20	421.2	(400 MHz, deuterium oxide) δ 7.31 - 7.23 (m, 2H), 7.22 - 7.05 (m, 5H), 6.81 (d, J = 7.6 Hz, 2H), 4.42 - 4.08 (m, 5H), 4.02 - 3.89 (m, 1H), 3.61 - 3.24 (m, 9H), 2.85 - 2.78 (m, 1H), 2.44 - 2.40 (m, 1H), 2.11 - 2.06 (m, 2H), 1.46 - 1.37 (m, 1H), 1.32 - 1.29 (m, 1H)
80	 (1R,2S)-2-phenyl-N-((1-(2-(4-(piperazin-1-yl)phenoxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine	Examples 10 and 20	407.2	(400 MHz, deuterium oxide) δ 7.36 (d, J = 9.2 Hz, 2H), 7.28 - 7.20 (m, 2H), 7.19 - 7.12 (m, 1H), 7.09 (d, J = 7.2 Hz, 2H), 7.02 - 6.94 (m, 2H), 4.40 - 4.25 (m, 2H), 4.23 - 4.00 (m, 4H), 3.74 - 3.67 (m, 4H), 3.66 - 3.61 (m, 1H), 3.61 - 3.54 (m, 6H), 3.51 - 3.46 (m, 1H), 3.42 - 3.31 (m, 1H), 2.92 - 2.82 (m, 1H), 2.49 - 2.38 (m, 1H), 1.49 - 1.39 (m, 1H), 1.34 - 1.30 (m, 1H)
81	 (1R,2S)-N-((1-(2-(4-(4-methylpiperazin-1-yl)phenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine	Examples 10 and 20	421.2	(400 MHz, deuterium oxide) δ 7.33 - 7.20 (m, 4H), 7.18 - 7.11 (m, 1H), 7.08 (d, J = 7.2 Hz, 2H), 7.02 - 6.92 (m, 2H), 4.41 - 4.24 (m, 2H), 4.23 - 4.00 (m, 4H), 3.86 - 3.66 (m, 4H), 3.65 - 3.27 (m, 9H), 2.93 (s, 3H), 2.91 - 2.81 (m, 1H), 2.45 - 2.41 (m, 1H), 1.48 - 1.39 (m, 1H), 1.36 - 1.26 (m, 1H)

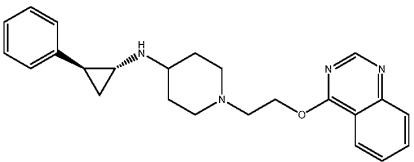
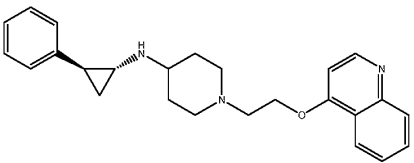
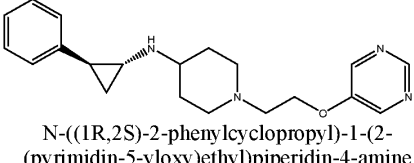
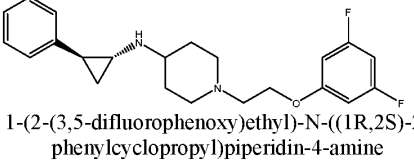
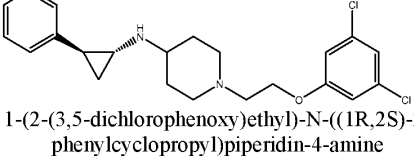
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
82	 1-(4-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)piperazin-1-yl)ethan-1-one	Examples 10 and 20	449.3	(400 MHz, deuterium oxide) □ 7.48 (d, <i>J</i> = 9.2 Hz, 2H), 7.26 - 7.18 (m, 2H), 7.16 - 7.10 (m, 1H), 7.08 (d, <i>J</i> = 7.2 Hz, 2H), 7.05 - 6.98 (m, 2H), 4.37 - 4.26 (m, 2H), 4.21 - 4.01 (m, 4H), 3.98 - 3.82 (m, 4H), 3.71 - 3.52 (m, 7H), 3.49 - 3.47 (m, 1H), 3.39 - 3.28 (m, 1H), 2.91 - 2.81 (m, 1H), 2.44 - 2.41 (m, 1H), 2.09 (s, 3H), 1.49 - 1.39 (m, 1H), 1.33 - 1.30 (m, 1H)
83	 N,6-dimethyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)pyridin-3-amine	Example 11	365.2	(400MHz, METHANOL- <i>d</i> ₄) δ = 7.96 - 7.95 (d, <i>J</i> = 3.2 Hz, 1H), 7.28 - 7.25 (m, 3H), 7.17 - 7.15 (m, 2H), 7.11 - 7.09 (m, 2H), 3.61 - 3.59 (m, 2H), 3.26 (m, 2H), 3.12 (m, 1H), 2.97 (s, 3H), 2.86 (m, 2H), 2.63 - 2.61 (m, 3H), 2.42 (s, 3H), 2.17 - 2.11 (m, 3H), 1.70 - 1.67 (m, 2H), 1.30 - 1.22 (m, 2H).
84	 1-(2-((5-methylpyridin-2-yl)oxy)ethyl)-N-(((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Scheme 2b	352.3	(400 MHz, METHANOL+D ₂ O- <i>d</i> ₄) δ = 8.10 (s, 1H), 8.05 - 8.03 (br d, <i>J</i> = 8.4 Hz, 1H), 7.35 - 7.29 (m, 2H), 7.25 - 7.19 (m, 4H), 4.76 - 4.74 (m, 2H), 3.88 - 3.85 (br d, <i>J</i> = 12.4 Hz, 2H), 3.76 - 3.72 (m, 3H), 3.42 - 3.34 (m, 2H), 3.01 - 2.99 (m, 1H), 2.57 - 2.47 (m, 3H), 2.36 (s, 3H), 2.20 - 2.17 (m, 2H), 1.61 - 1.58 (m, 1H), 1.47 - 1.45 (m, 1H)
85	 1-(2-((6-methylpyridin-3-yl)oxy)ethyl)-N-(((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Scheme 2b	352.1	(400 MHz, D ₂ O) δ = 8.31 (d, <i>J</i> = 2.0 Hz, 1H), 8.04 (d, <i>J</i> = 2.0, 1H), 7.76 - 7.74 (d, <i>J</i> = 8.8 Hz, 1H), 7.36 - 7.34 (m, 2H), 7.32 - 7.26 (m, 1H), 7.17 - 7.15 (br d, <i>J</i> = 7.6 Hz, 2H), 4.55 - 4.53 (m, 2H), 3.82 - 3.69 (m, 5H), 3.28 - 3.25 (m, 2H), 2.99 - 2.97 (m, 1H), 2.65 (s, 3H), 2.50 - 2.43 (m, 3H), 2.05 (br s, 2H), 1.52 - 1.44 (m, 2H)
86	 1-(2-((4-bromophenyl)(methyl)amino)ethyl)-N-(((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Scheme 2b	428.0; 430.0	(400 MHz, Methanol- <i>d</i> ₄) δ 7.46 (d, <i>J</i> = 8.8 Hz, 2H), 7.37 - 7.30 (m, 2H), 7.29 - 7.19 (m, 3H), 7.06 (d, <i>J</i> = 8.8 Hz, 2H), 3.96 - 3.91 (m, 2H), 3.85 - 3.67 (m, 3H), 3.43 - 3.37 (m, 2H), 3.34 - 3.26 (m, 2H), 3.12 - 3.04 (m, 4H), 2.62 - 2.58 (m, 1H), 2.49 - 2.43 (m, 2H), 2.31 - 2.12 (m, 2H), 1.67 - 1.58 (m, 1H), 1.48 - 1.45 (m, 1H)

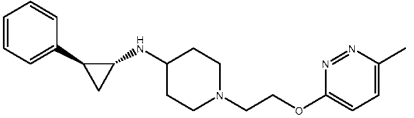
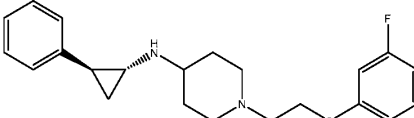
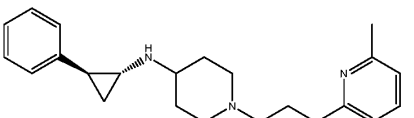
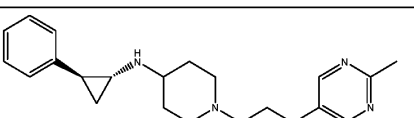
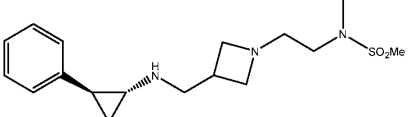
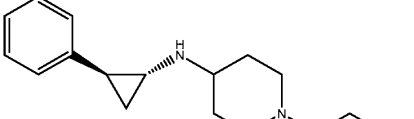
Ex. #	Structure	Method	LCMS [M+] Observed	¹ H NMR
87	 N-(methylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide	Scheme 3b	458.1	¹ H NMR: 500 MHz, DMSO-d ₆ , δ (ppm): 11.98 (bs, 1H), 10.82 (bs, 1H), 9.93 (bs, 2H), 7.97 (d, <i>J</i> = 9.0 Hz, 2H), 7.33-7.29 (m, 2H), 7.25-7.18 (m, 3H), 7.12 (d, <i>J</i> = 9.0 Hz, 2H), 4.49 (bt, 2H), 3.68-3.66 (m, 2H), 3.50 (bs, 4H), 3.36 (s, 3H), 3.14 (bs, 2H), 2.98 (bs, 1H), 2.56 (bs, 1H), 2.30 (bs, 2H), 2.11 (bs, 1H), 1.58 (bs, 1H), 1.32-1.28 (m, 1H).
88	 N-(ethylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide	Scheme 3b	472.2	¹ H NMR: 500 MHz, DMSO-d ₆ , δ (ppm): 11.87 (bs, 1H), 10.94 (bs, 1H), 10.01 (bs, 2H), 7.97 (d, <i>J</i> = 8.9 Hz, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 7.12 (d, <i>J</i> = 9.0 Hz, 2H), 4.50 (bt, 2H), 3.68-3.66 (m, 2H), 3.53-3.48 (m, 6H), 3.14 (bs, 2H), 2.97 (bs, 1H), 2.58 (bs, 1H), 2.31 (bs, 2H), 2.12 (bs, 1H), 1.59 (bs, 1H), 1.31-1.27 (m, 1H), 1.25 (t, <i>J</i> = 7.4 Hz, 3H).
89	 (1S,2R)-N-((1-(2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)oxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine	Example 20	422.3	(400 MHz, METHANOL-d ₄) δ = 7.79 - 7.77 (m, 1H), 7.74 (br d, <i>J</i> = 8.4 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.25 - 7.21 (m, 3H), 7.09 - 7.06 (br d, <i>J</i> = 9.2 Hz, 1H), 4.56 (br s, 2H), 4.44 - 4.24 (m, 4H), 3.80 - 3.77 (m, 5H), 3.64 - 3.61 (m, 3H), 3.39 (m, 1H), 3.33 (m, 1H), 3.28 (m, 1H), 3.17 - 3.14 (m, 2H), 3.03 (m, 1H), 2.97 (s, 3H), 2.61 - 2.57 (m, 1H), 1.63 - 1.58 (m, 1H), 1.42 - 1.39 (q, <i>J</i> = 6.8 Hz, 1H).
90	 2-(4-(2-(3-(((1S,2R)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)acetic acid	Scheme 2a	381.2	(400 MHz, deuterium oxide) δ 7.31 - 7.18 (m, 5H), 7.12 (d, <i>J</i> = 7.6 Hz, 2H), 6.87 (d, <i>J</i> = 8.8 Hz, 2H), 4.42 - 4.30 (m, 2H), 4.22 - 4.02 (m, 4H), 3.68 - 3.53 (m, 5H), 3.52 - 3.49 (m, 1H), 3.42 - 3.31 (m, 1H), 2.93 - 2.85 (m, 1H), 2.47 - 2.44 (m, 1H), 1.50 - 1.43 (m, 1H), 1.40 - 1.33 (m, 1H).
91	 3-(4-(methyl(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one	Example 20	449.3	(400 MHz, Deuterium oxide) δ 7.34 - 7.28 (m, 4H), 7.27 - 7.20 (m, 1H), 7.19 - 7.10 (m, 4H), 4.39 (t, <i>J</i> = 5.4 Hz, 2H), 3.83 (t, <i>J</i> = 7.4 Hz, 2H), 3.72 - 3.53 (m, 5H), 3.39 - 3.28 (m, 2H), 3.20 - 3.00 (m, 5H), 2.96 - 2.90 (m, 1H), 2.49 - 2.32 (m, 3H), 2.17 - 2.09 (m, 2H), 2.04 - 1.88 (m, 2H), 1.50 - 1.37 (m, 2H).

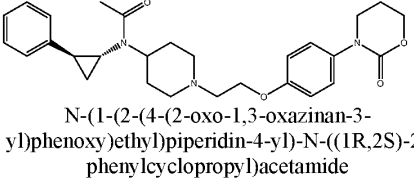
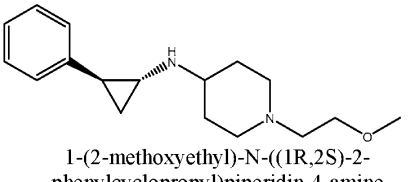
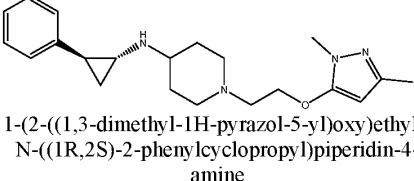
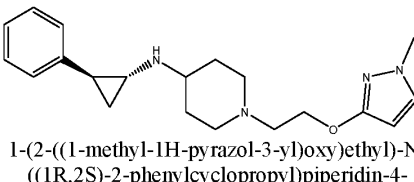
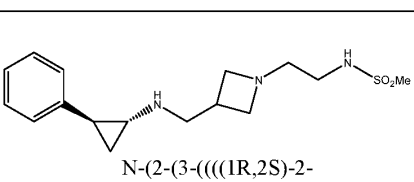
Ex. #	Structure	Method	LCMS [M+] Observed	¹ H NMR
92	 4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)benzoic acid	Scheme 2a	367.0	(400 MHz, Deuterium Oxide) δ = 7.99 - 7.97 (m, 2H), 7.32 - 7.24 (m, 3H), 7.17 - 7.15 (m, 2H), 7.01 - 6.98 (d, J = 8.8 Hz, 2H), 4.42 - 4.37 (m, 2H), 4.27 - 4.11 (m, 4H), 3.77 - 3.70 (m, 1H), 3.69 - 3.60 (m, 2H), 3.56 - 3.54 (d, J = 6.8 Hz, 1H), 3.43 - 3.41 (m, 1H), 2.94 - 2.92 (m, 1H), 2.53 - 2.48 (m, 1H), 1.52 - 1.43 (m, 1H), 1.41 - 1.40 (m, 1H)
93	 2-(4'-(2-(3-(((1S,2R)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)-[1,1'-biphenyl]-4-yl)-N-(phenylsulfonyl)acetamide	Scheme 3a	520.3	(400 MHz, deuterium oxide) δ 7.83 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.51 - 7.47 (m, 2H), 7.26 - 7.20 (m, 2H), 7.16 - 7.06 (m, 3H), 7.00 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 4.35 - 4.25 (m, 2H), 4.17 - 3.98 (m, 4H), 3.62 - 3.45 (m, 6H), 3.37 - 3.28 (m, 1H), 2.90 - 2.82 (m, 1H), 2.44 - 2.41 (m, 1H), 1.48 - 1.41 (m, 1H), 1.37 - 1.31 (m, 1H)
94	 3-(6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)pyridin-3-yl)-1,3-oxazinan-2-one	Example 20	437.2	(400 MHz, D ₂ O) δ = 8.11 (d, J = 2.8 Hz, 1H), 7.80 - 7.78 (m, 1H), 7.36 - 7.32 (m, 2H), 7.28 - 7.27 (m, 1H), 7.17 - 7.15 (d, J = 7.6 Hz, 2H), 7.00 - 6.98 (d, J = 8.8 Hz, 1H), 4.62 - 4.60 (m, 2H), 4.46 - 4.43 (t, J = 5.2 Hz, 2H), 3.85 - 3.82 (br d, J = 12.0 Hz, 2H), 3.68 - 3.62 (m, 5H), 3.26 - 3.15 (m, 2H), 2.98 - 2.96 (m, 1H), 2.49 - 2.43 (m, 3H), 2.19 - 2.16 (m, 2H), 2.01 (m, 2H), 1.50 - 1.43 (m, 2H)
95	 N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(p-tolylethoxy)piperidin-4-amine	Example 11	351.3	(400 MHz, deuterium oxide) δ 7.36 - 7.26 (m, 2H), 7.26 - 7.18 (m, 1H), 7.17 - 7.09 (m, 4H), 6.89 - 6.81 (m, 2H), 4.27 (t, J = 4.8 Hz, 2H), 3.80 - 3.57 (m, 3H), 3.56 - 3.48 (m, 2H), 3.23 - 3.08 (m, 2H), 3.02 - 2.89 (m, 1H), 2.49 - 2.31 (m, 3H), 2.23 - 2.14 (m, 3H), 2.07 - 1.86 (m, 2H), 1.50 - 1.36 (m, 2H)
96	 3-(4-(2-(4-(methyl((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one	Example 20	450.3	(400 MHz, D ₂ O) δ = 7.34 - 7.29 (m, 2H), 7.27 - 7.23 (m, 3H), 7.16 (br s, 2H), 7.02 - 7.00 (m, 2H), 4.41 - 4.35 (m, 4H), 3.81 (m, 2H), 3.63 - 3.55 (m, 5H), 3.20 - 3.15 (m, 3H), 3.02 (s, 3H), 2.60 (m, 3H), 2.16 - 2.11 (m, 4H), 1.55 - 1.54 (m, 2H).

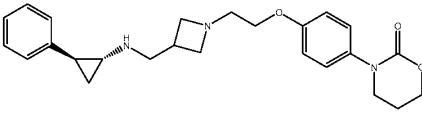
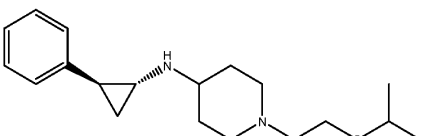
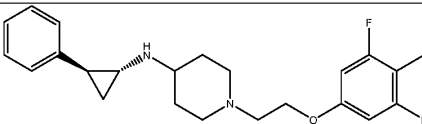
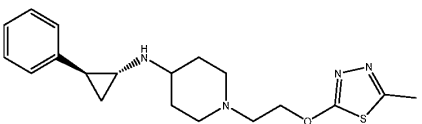
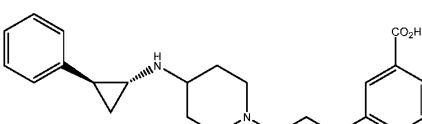
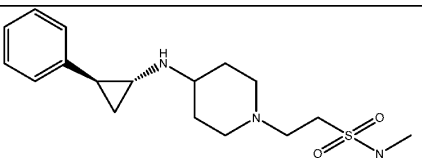
Ex. #	Structure	Method	LCMS [M+] Observed	¹ H NMR
97	 3-(5-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)pyridin-2-yl)-1,3-oxazinan-2-one	Example 20	437.2	(400 MHz, D ₂ O) δ = 8.20 - 8.19 (d, <i>J</i> = 3.2 Hz, 1H), 7.81 - 7.78 (m, 1H), 7.58 - 7.56 (d, <i>J</i> = 9.2 Hz, 1H), 7.32 - 7.25 (m, 3H), 7.16 - 7.14 (d, <i>J</i> = 7.2 Hz, 2H), 4.51 - 4.45 (br s, 4H), 3.83 - 3.63 (m, 7H), 3.22 - 3.20 (m, 2H), 2.98 - 2.97 (m, 1H), 2.48 - 2.46 (m, 3H), 2.22 - 2.19 (m, 2H), 2.03 (m, 2H), 1.51 - 1.42 (m, 2H).
98	 2-(4-(2-(1-methyl-3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)-2-phenylcyclopropyl)amino)methyl)-2,4-azetidin-1-yl)ethoxy)phenyl)-N-(methylsulfonyl)acetamide	Scheme 3a	472.2	(400 MHz, deuterium oxide) δ 7.38 - 7.31 (m, 2H), 7.30 - 7.19 (m, 5H), 7.00 (d, <i>J</i> = 8.8 Hz, 2H), 4.71 - 4.63 (m, 2H), 4.50 - 4.40 (m, 4H), 4.00 - 3.93 (m, 2H), 3.77 - 3.68 (m, 1H), 3.67 - 3.60 (m, 2H), 3.41 - 3.37 (m, 2H), 3.35 (s, 3H), 3.23 (s, 3H), 3.05 - 3.00 (m, 1H), 2.65 - 2.59 (m, 1H), 1.66 - 1.60 (m, 1H), 1.45 - 1.41 (m, 1H)
99	 N-methyl-1-(2-((6-methylpyridin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	366.2	(400 MHz, D ₂ O) δ = 8.31 (d, <i>J</i> = 2.8 Hz, 1H), 8.06 - 8.03 (m, 1H), 7.77 - 7.75 (d, <i>J</i> = 8.8 Hz, 1H), 7.35 - 7.34 (m, 2H), 7.30 - 7.28 (m, 1H), 7.18 - 7.16 (m, 2H), 4.55 - 4.53 (m, 2H), 3.84 - 3.81 (m, 3H), 3.69 - 3.67 (m, 2H), 3.26 (m, 2H), 3.16 - 3.15 (m, 1H), 3.04 (s, 3H), 2.65 (s, 3H), 2.62 - 2.39 (m, 3H), 2.20 - 2.16 (m, 2H), 1.62 - 1.55 (m, 2H).
100	 N-methyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)acetamide	Example 39	316.1	(400 MHz, CD ₃ OD) δ = 7.25 - 7.18 (m, 2H), 7.15 - 7.08 (m, 1H), 7.03 (m, <i>J</i> = 7.6 Hz, 2H), 3.53 - 3.44 (m, 2H), 3.05 (s, 2H), 3.00 - 2.90 (m, 3H), 2.70 - 2.59 (m, 1H), 2.56 - 2.46 (m, 2H), 2.33 - 2.27 (m, 1H), 2.22 - 2.00 (d, 6H), 1.98 - 1.81 (m, 3H), 1.50 - 1.38 (m, 2H), 1.09 - 0.97 (m, 2H).
101	 (1R,2S)-N-((1-(2-((6-methylpyridin-3-yl)oxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine	Example 11	338.1	(400 MHz, METHANOL- <i>d</i> ₄) δ = 8.08 (d, <i>J</i> = 2.8 Hz, 1H), 7.31 - 7.30 (m, 1H), 7.24 - 7.20 (m, 3H), 7.17 - 7.13 (m, 1H), 7.06 - 7.04 (m, 2H), 4.09 - 4.07 (t, <i>J</i> = 5.2 Hz, 2H), 3.77 - 3.73 (t, <i>J</i> = 8.4 Hz, 2H), 3.34 - 3.31 (s, 2H), 3.08 - 3.05 (t, <i>J</i> = 5.2 Hz, 2H), 2.96 - 2.94 (d, <i>J</i> = 7.2 Hz, 2H), 2.82 - 2.81 (m, 1H), 2.45 (s, 3H), 2.33 - 2.32 (m, 1H), 1.91 - 1.90 (m, 1H), 1.09 - 1.01 (m, 2H).

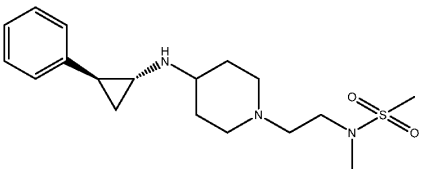
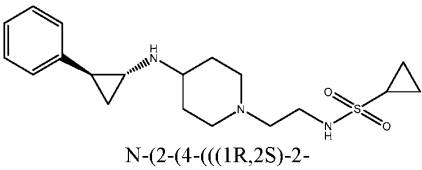
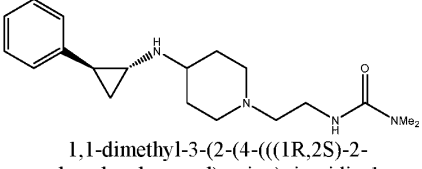
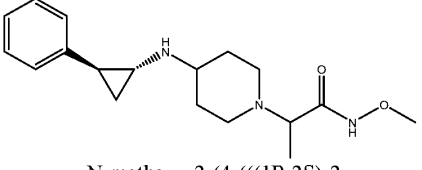
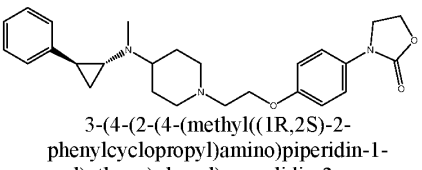
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
102	 4-(2-(1-methyl-3-((((1R,2S)-2-phenylcyclopropyl)amino)methyl)-2-phenylethoxy)-N-(methylsulfonyl)benzamide	Scheme 3a	458.1	(400 MHz, deuterium oxide) δ 7.29 - 7.20 (m, 2H), 7.19 - 7.13 (m, 1H), 7.12 - 7.04 (m, 4H), 6.94 - 6.86 (m, 2H), 4.37 - 4.24 (m, 2H), 4.20 - 3.99 (m, 4H), 3.65 - 3.43 (m, 6H), 3.38 - 3.26 (m, 1H), 2.92 - 2.81 (m, 1H), 2.47 - 2.33 (m, 3H), 1.86 - 1.73 (m, 4H), 1.48 - 1.38 (m, 1H), 1.37 - 1.27 (m, 1H)
103	 3-(5-(2-(3-((((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)pyridin-2-yl)-1,3-oxazinan-2-one	Example 20	423.1	(400 MHz, D ₂ O) δ = 8.05 - 8.03 (m, 1H), 7.51 (m, 1H), 7.43 - 7.41 (d, J =8.8 Hz, 1H), 7.26 - 7.24 (m, 2H), 7.18 - 7.16 (m, 1H), 7.10 - 7.08 (m, 2H), 4.43 - 4.40 (m, 2H), 4.33 - 4.42 (m, 6H), 3.72 - 3.69 (m, 3H), 3.60 - 3.55 (m, 2H), 3.49 - 3.47 (m, 1H), 3.34 (m, 1H), 2.86 - 2.85 (m, 1H), 2.43 (m, 1H), 2.18 - 2.14 (m, 2H), 1.44 - 1.43 (m, 1H), 1.35 - 1.33 (q, J =7.2 Hz, 1H)
104	 6-(2-(4-((((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-3,4-dihydroquinolin-2(1H)-one	Example 11	406.0	(400 MHz, Deuterium oxide) δ 7.34 - 7.28 (m, 2H), 7.27 - 7.21 (m, 1H), 7.13 (d, J =7.2 Hz, 2H), 6.86 - 6.77 (m, 3H), 4.29 - 4.24 (m, 2H), 3.50 - 3.48 (m, 1H), 3.85 - 3.48 (m, 4H), 3.26 - 3.07 (m, 2H), 2.97 - 2.93 (m, 1H), 2.89 - 2.81 (m, 2H), 2.53 - 2.33 (m, 5H), 2.09 - 1.90 (m, 2H), 1.52 - 1.37 (m, 2H)
105	 5-(2-(4-((((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)indolin-2-one	Example 11	392.2	(400 MHz, methanol-d ₄) δ , 7.39 - 7.29 (m, 2H), 7.28 - 7.17 (m, 3H), 7.04 (d, J = 2.0 Hz, 1H), 6.97 - 6.88 (m, 1H), 6.87 - 6.81 (m, 1H), 4.42 - 4.35 (m, 2H), 3.88 (br d, J = 12.4 Hz, 2H), 3.82 - 3.73 (m, 1H), 3.67 - 3.59 (m, 2H), 3.34 (br s, 2H), 3.31 (br s, 2H), 3.09 - 3.01 (m, 1H), 2.60 (br s, 1H), 2.50 (br t, J = 11.6 Hz, 2H), 2.37 - 2.15 (m, 2H), 1.67 - 1.58 (m, 1H), 1.49 - 1.43 (m, 1H)
106	 1-(2-(3-fluoro-4-methylphenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	369.1	(400MHz, methanol-d ₄) δ , 7.38 - 7.29 (m, 2H), 7.30 - 7.27 (m, 1H), 7.24 - 7.19 (m, 2H), 7.18 - 7.16 (m, 1H), 6.81 - 6.71 (m, 2H), 4.43 - 4.34 (m, 2H), 3.85 (br d, J = 11.6 Hz, 2H), 3.73 (br s, 1H), 3.62 (br s, 2H), 3.30 - 3.22 (m, 2H), 3.03 (td, J = 4.0, 7.6 Hz, 1H), 2.56 (br s, 1H), 2.47 (br s, 2H), 2.25 - 2.16 (m, 5H), 1.60 (br s, 1H), 1.47 - 1.42 (m, 1H)

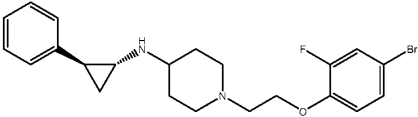
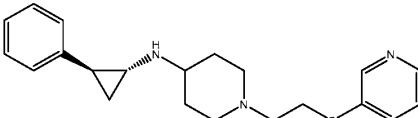
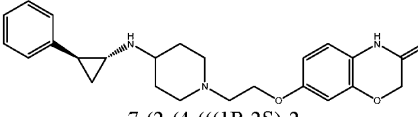
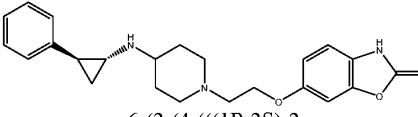
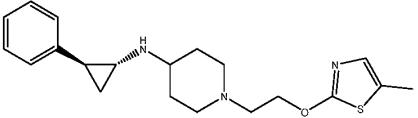
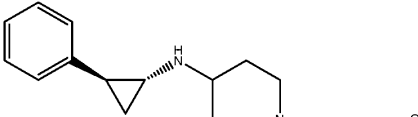
Ex. #	Structure	Method	LCMS [M+] Observed	¹ H NMR
107	 N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(quinazolin-4-yloxy)ethyl)piperidin-4-amine	Example 36	389.5	(400 MHz, METHANOL-d ₄) δ = 8.74 (s, 1H), 8.27 - 8.25 (d, J=8.0 Hz, 1H), 7.94 - 7.90 (m, 2H), 7.69 - 7.67 (m, 1H), 7.23 - 7.19 (m, 2H), 7.12 - 7.10 (m, 1H), 7.03 - 7.02 (d, J=7.2 Hz, 2H), 4.79 - 4.76 (t, J=5.2 Hz, 2H), 3.10 - 2.96 (m, 2H), 2.94 - 2.93 (m, 2H), 2.74 - 2.59 (m, 1H), 2.30 - 2.28 (m, 3H), 1.94 - 1.88 (m, 3H), 1.51 - 1.48 (m, 2H), 1.06 - 1.00 (m, 2H).
108	 N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(quinolin-4-yloxy)ethyl)piperidin-4-amine	Example 36	388.2	(400 MHz, Methanol-d ₄) δ 8.69 (d, J=5.2 Hz, 1H), 8.28 (d, J=8.4 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 7.77 (t, J=7.6 Hz, 1H), 7.62 - 7.55 (m, 1H), 7.26 - 7.21 (m, 2H), 7.15 - 7.10 (m, 1H), 7.09 - 7.00 (m, 3H), 4.44 (t, J=5.2 Hz, 2H), 3.16 - 3.08 (m, 2H), 3.01 (t, J=5.4 Hz, 2H), 2.78 - 2.64 (m, 1H), 2.42 - 2.26 (m, 3H), 2.07 - 1.78 (m, 3H), 1.62 - 1.47 (m, 2H), 1.14 - 1.00 (m, 2H)
109	 N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(pyrimidin-5-yloxy)ethyl)piperidin-4-amine	Example 11	339.1	(400 MHz, CHLOROFORM-d) δ = 8.87 (s, 1H), 8.44 (s, 2H), 7.37 - 7.13 (m, 4H), 7.04 (d, J=7.0 Hz, 2H), 4.21 (t, J=5.7 Hz, 2H), 2.96 (br d, J=11.4 Hz, 2H), 2.89 - 2.78 (m, 2H), 2.73 - 2.61 (m, 1H), 2.41 - 2.33 (m, 1H), 2.21 (br t, J=11.4 Hz, 2H), 2.01 - 1.84 (m, 3H), 1.54 - 1.38 (m, 2H), 1.14 - 0.96 (m, 2H)
110	 1-(2-(3,5-difluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	372.9	(400 MHz, deuterium oxide) δ 7.34 - 7.27 (m, 2H), 7.26 - 7.20 (m, 1H), 7.13 (d, J=7.6 Hz, 2H), 6.60 - 6.52 (m, 3H), 4.31 (t, J=4.6 Hz, 2H), 3.80 - 3.60 (m, 3H), 3.57 - 3.53 (m, 2H), 3.26 - 3.07 (m, 2H), 2.94 - 2.92 (m, 1H), 2.50 - 2.32 (m, 3H), 2.02 - 1.87 (m, 2H), 1.52 - 1.36 (m, 2H)
111	 1-(2-(3,5-dichlorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	406.9	(400 MHz, deuterium oxide) δ 7.35 - 7.28 (m, 2H), 7.27 - 7.20 (m, 1H), 7.17 - 7.07 (m, 3H), 6.94 (d, J=1.6 Hz, 2H), 4.31 (t, J=4.6 Hz, 2H), 3.79 - 3.62 (m, 3H), 3.62 - 3.54 (m, 2H), 3.24 - 3.10 (m, 2H), 2.95 - 2.92 (m, 1H), 2.50 - 2.33 (m, 3H), 2.06 - 1.89 (m, 2H), 1.50 - 1.37 (m, 2H)

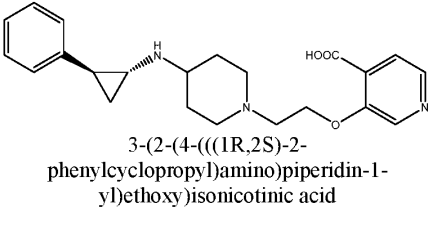
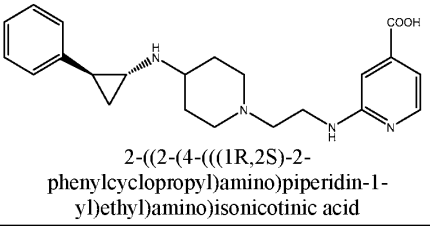
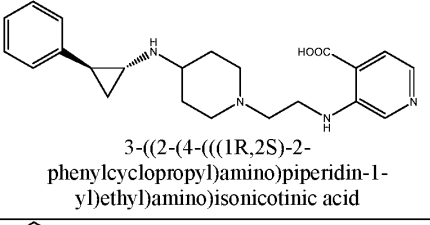
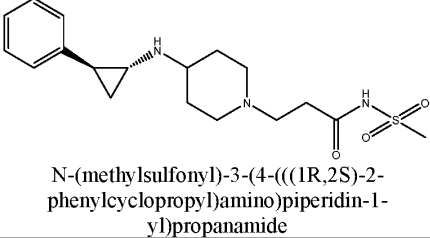
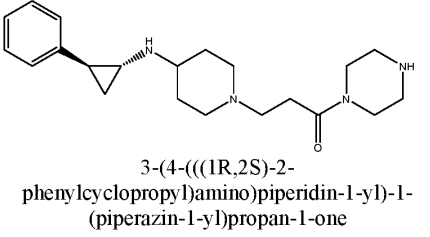
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
112	 1-(2-((6-methylpyridazin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 36	353.2	(400MHz, CD ₃ OD) δ = 7.51-7.47 (m, 1H), 7.24-7.20 (m, 2H), 7.13-7.09 (m, 2H), 7.04-7.02 (m, 2H), 4.58-4.55 (t, J = 5.6 Hz, 2H), 3.04-3.01 (m, 2H), 2.84-2.01 (t, J = 5.6 Hz, 2H), 2.69-2.60 (m, 1H), 2.56 (s, 3H), 2.32-2.28 (m, 1H), 2.21-2.15 (m, 2H), 1.94-1.87 (m, 3H), 1.53-1.41 (m, 2H), 1.08-0.99 (m, 2H).
113	 1-(2-(3-fluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	355.1	(400 MHz, CHLOROFORM-d) δ = 7.36 - 7.22 (m, 6H), 6.88 - 6.78 (s, 3H), 4.45 - 4.42 (t, J=4.8 Hz, 2H), 3.88 - 3.65 (m, 5H), 3.36 - 3.27 (m, 2H), 3.06 - 3.03 (m, 1H), 2.57 - 2.48 (m, 3H), 2.20 - 2.17 (m, 2H), 1.61 - 1.47 (m, 2H).
114	 1-(2-((6-methylpyridin-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 36	352.2	(400MHz, CD ₃ OD) δ = 7.64-7.60 (t, J = 7.6 Hz, 1H), 7.33-7.17 (m, 5H), 6.89 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.69-4.67 (m, 2H), 3.88-3.85 (m, 2H), 3.73-3.61 (m, 3H), 2.29-3.23 (m, 2H), 3.03-2.99 (m, 1H), 2.53-2.43 (m, 6H), 2.16-2.07 (m, 2H), 1.57-1.52 (m, 1H), 1.47-1.42 (m, 1H).
115	 1-(2-((2-methylpyrimidin-5-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	353.1	(400 MHz, D ₂ O) δ = 8.69 - 8.68 (d, J = 2.8 Hz, 2H), 7.35 - 7.24 (m, 3H), 7.16 - 7.14 (d, J = 7.6 Hz, 2H), 4.57 - 4.55 (t, J = 4.4 Hz, 2H), 3.83 - 3.68 (m, 5H), 3.23 (m, 2H), 2.98 - 2.96 (m, 1H), 2.70 (s, 3H), 2.50 - 2.43 (m, 3H), 2.04 (br s, 2H), 1.51 - 1.41 (m, 2H).
116	 N-methyl-N-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)methanesulfonamide	Example 41	338.1	(400 MHz, CD ₃ OD) δ = 7.25-7.03 (m, 5H), 3.51-3.45 (m, 2H), 3.11-3.06 (m, 2H), 2.97-2.94 (m, 2H), 2.89-2.87 (m, 2H), 2.85-2.82 (m, 6H), 2.69-2.62 (m, 3H), 2.29-2.26 (m, 1H), 1.90-1.85 (m, 1H), 1.97-0.97 (m, 2H).
117	 2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethan-1-ol	Example 36	261.3	(400 MHz, METHANOL-d ₄) δ = 7.25 - 7.22 (m, 2H), 7.14 - 7.06 (m, 1H), 7.06 - 7.04 (m, 2H), 3.69 - 3.66 (t, J=6.4 Hz, 2H), 2.99 - 2.96 (m, 2H), 2.66 (m, 1H), 2.54 - 2.51 (t, J=6.4 Hz, 2H), 2.32 (m, 1H), 2.13 - 2.12 (m, 2H), 1.92 - 1.90 (m, 3H), 1.57 - 1.40 (m, 2H), 1.08 - 1.02 (m, 2H).

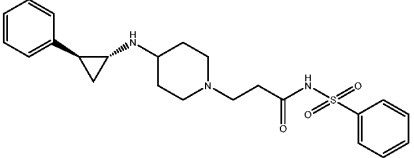
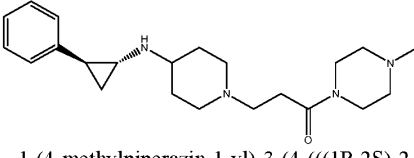
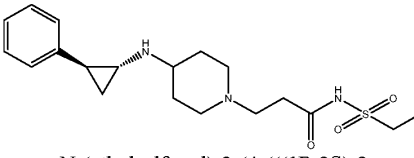
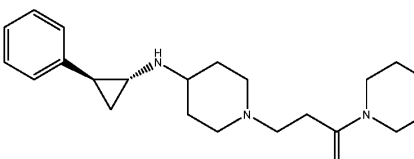
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
118	 N-(1-(2-(4-(2-oxo-1,3-oxazinan-3-yl)phenoxy)ethyl)piperidin-4-yl)-N-((1R,2S)-2-phenylcyclopropyl)acetamide	Example 20	478.1	(400 MHz, METHANOL-d ₄) δ = 7.33 - 7.29 (m, 4H), 7.20 - 7.18 (m, 3H), 7.09 - 7.06 (d, <i>J</i> = 8.8 Hz, 2H), 4.46 - 4.41 (m, 4H), 4.14 (m, 1H), 3.75 - 3.69 (m, 4H), 3.61 - 3.59 (m, 2H), 3.25 (m, 2H), 3.02 (br s, 1H), 2.78 - 2.61 (m, 1H), 2.58 - 2.44 (m, 1H), 2.37 (m, 1H), 2.24 - 2.18 (m, 5H), 2.07 - 2.03 (m, 2H), 1.62 - 1.61 (m, 1H), 1.46 - 1.45 (m, 1H).
119	 1-(2-methoxyethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 36	275.2	(400 MHz, Methanol-d ₄) δ 7.28 - 7.21 (m, 2H), 7.17 - 7.10 (m, 1H), 7.09 - 6.99 (m, 2H), 3.57 - 3.49 (m, 2H), 3.34 - 3.32 (m, 3H), 3.07 - 2.92 (m, 2H), 2.69 - 2.52 (m, 3H), 2.34 - 2.30 (m, 1H), 2.20 - 2.03 (m, 2H), 1.98 - 1.85 (m, 3H), 1.56 - 1.43 (m, 2H), 1.13 - 1.00 (m, 2H).
120	 1-(2-((1,3-dimethyl-1H-pyrazol-5-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	355.2	(400 MHz, Methanol-d ₄) δ 7.29 - 7.18 (m, 2H), 7.16 - 7.09 (m, 1H), 7.08 - 7.01 (m, 2H), 5.48 (s, 1H), 4.18 (t, <i>J</i> =5.4 Hz, 2H), 3.53 (s, 3H), 3.02 - 2.96 (m, 2H), 2.78 (t, <i>J</i> =5.6 Hz, 2H), 2.73 - 2.55 (m, 1H), 2.34 - 2.29 (m, 1H), 2.21 - 2.13 (m, 5H), 2.00 - 1.85 (m, 3H), 1.65 - 1.42 (m, 2H), 1.11 - 1.00 (m, 2H)
121	 1-(2-((1-methyl-1H-pyrazol-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	341.2	(400 MHz, Methanol-d ₄) δ 7.34 (d, <i>J</i> =2.0 Hz, 1H), 7.28 - 7.19 (m, 2H), 7.17 - 7.09 (m, 1H), 7.09 - 7.01 (m, 2H), 5.66 (d, <i>J</i> =2.4 Hz, 1H), 4.21 (t, <i>J</i> =5.6 Hz, 2H), 3.72 (s, 3H), 3.03 - 3.00 (m, 2H), 2.76 (t, <i>J</i> =5.4 Hz, 2H), 2.71 - 2.53 (m, 1H), 2.34 - 2.29 (m, 1H), 2.21 - 2.15 (m, 2H), 1.99 - 1.74 (m, 3H), 1.65 - 1.43 (m, 2H), 1.11 - 1.00 (m, 2H)
122	 N-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)methanesulfonamide	Example 41	324.1	(400 MHz, methanol-d ₄) δ = 7.27 - 7.21 (m, 2H), 7.16 - 7.11 (m, 1H), 7.08 - 7.04 (m, 2H), 3.51 (t, <i>J</i> = 8.0 Hz, 2H), 3.04 (t, <i>J</i> = 6.8 Hz, 2H), 2.99 (br t, <i>J</i> = 6.4 Hz, 2H), 2.95 (s, 3H), 2.91 (d, <i>J</i> = 7.6 Hz, 2H), 2.70 (td, <i>J</i> = 7.2, 14.4 Hz, 1H), 2.62 (t, <i>J</i> = 6.8 Hz, 2H), 2.30 (td, <i>J</i> = 3.6, 7.2 Hz, 1H), 1.90 (ddd, <i>J</i> = 3.2, 6.0, 9.2 Hz, 1H), 1.10 - 0.98 (m, 2H).

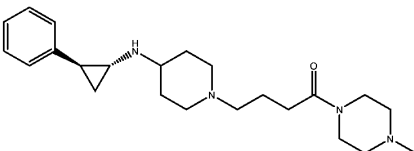
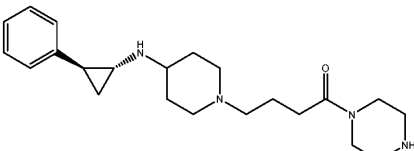
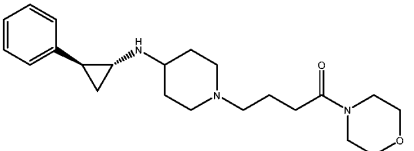
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
123	 3-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)-1,3-oxazin-2-one	Example 20	423.0	(400 MHz, METHANOL- <i>d</i> ₄) δ = 8.18 (d, <i>J</i> = 2.4 Hz, 1H), 7.76 - 7.74 (dd, <i>J</i> = 2.8, 8.8 Hz, 1H), 7.34 - 7.18 (m, 5H), 6.91 - 6.88 (d, <i>J</i> = 9.2 Hz, 1H), 4.59 - 4.56 (m, 2H), 4.49 - 4.46 (m, 4H), 4.21 (br s, 2H), 3.74 - 3.69 (m, 4H), 3.60 - 3.58 (br d, <i>J</i> = 6.8 Hz, 2H), 3.44 - 3.35 (m, 1H), 2.99 - 2.97 (m, 1H), 2.53 (m, 1H), 2.25 - 2.2 (m, 2H), 1.56 - 1.52 (m, 1H), 1.43 - 1.40 (q, <i>J</i> = 6.8 Hz, 1H).
124	 1-(2-isopropoxyethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 36	303.1	(400 MHz, CD ₃ OD) δ = 7.27 - 7.20 (m, 2H), 7.16 - 7.10 (m, 1H), 7.08 - 7.02 (m, 2H), 3.63 - 3.56 (m, 3H), 2.98 (d, <i>J</i> = 12.4 Hz, 2H), 2.70 - 2.61 (m, 1H), 2.56 (t, <i>J</i> = 6.0 Hz, 2H), 2.32 (m, 1H), 2.13 (tt, <i>J</i> = 2.8, 12.0 Hz, 2H), 1.98 - 1.86 (m, 3H), 1.57 - 1.42 (m, 2H), 1.16 (d, <i>J</i> = 6.0 Hz, 6H), 1.10 - 1.00 (m, 2H).
125	 1-(2-(3,5-difluoro-4-methylphenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	387.1	(400 MHz, METHANOL- <i>d</i> ₄) δ = 7.40 - 7.18 (m, 5H), 6.74 - 6.63 (m, 2H), 4.48 - 4.32 (m, 2H), 3.92 - 3.58 (m, 5H), 3.31 - 3.08 (m, 2H), 2.94 - 2.91 (t, <i>J</i> = 7.6 Hz, 1H), 2.45 - 2.35 (m, 3H), 2.04 - 1.91 (m, 5H), 1.53 - 1.42 (m, 2H).
126	 1-(2-((5-methyl-1,3,4-thiadiazol-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	359.1	(400 MHz, CD ₃ OD) δ = 7.14 - 7.10 (m, 2H), 7.03 - 6.99 (m, 1H), 6.94 - 6.92 (d, <i>J</i> = 7.6 Hz, 2H), 4.49 - 4.46 (t, <i>J</i> = 5.4 Hz, 2H), 2.90 - 2.87 (br d, <i>J</i> = 11.2 Hz, 2H), 2.73 - 2.62 (t, <i>J</i> = 5.4 Hz, 2H), 2.59 - 2.51 (m, 1H), 2.49 (s, 3H), 2.30 (td, <i>J</i> = 3.6, 7.6 Hz, 1H), 2.22 - 2.08 (m, 2H), 1.98 - 1.83 (m, 3H), 1.54 - 1.40 (m, 2H), 1.12 - 0.97 (m, 2H).
127	 2-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)isonicotinic acid	Example 11	382.1	(400 MHz, METHANOL- <i>d</i> ₄) δ = 8.14 - 8.13 (m, 1H), 7.40 - 7.39 (d, <i>J</i> = 5.2 Hz, 1H), 7.28 - 7.24 (m, 3H), 7.17 - 7.07 (m, 3H), 4.61 - 4.58 (m, 2H), 3.48 - 3.45 (m, 2H), 3.30 - 3.28 (m, 2H), 3.04 (m, 1H), 2.84 (m, 2H), 2.47 - 2.46 (m, 1H), 2.17 - 2.15 (m, 2H), 2.03 - 2.02 (m, 1H), 1.76 - 1.72 (m, 2H), 1.19 - 1.13 (m, 2H).
128	 N-methyl-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethane-1-sulfonamide	Example 39	338.1	(400 MHz, methanol- <i>d</i> ₄) δ = 7.26 - 7.22 (m, 2H), 7.16 - 7.11 (m, 1H), 7.08 - 7.02 (m, 2H), 3.29 - 3.20 (m, 2H), 2.95 (br d, <i>J</i> = 12.0 Hz, 2H), 2.84 - 2.77 (m, 2H), 2.75 - 2.71 (m, 3H), 2.70 - 2.63 (m, 1H), 2.32 (ddd, <i>J</i> = 3.2, 4.4, 7.2 Hz, 1H), 2.20 - 2.09 (m, 2H), 2.02 - 1.87 (m, 3H), 1.55 - 1.40 (m, 2H), 1.13 - 0.99 (m, 2H).

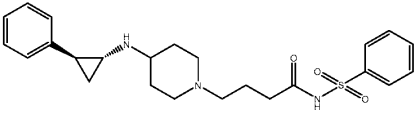
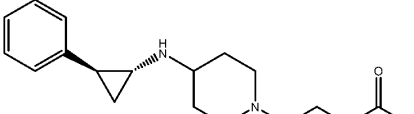
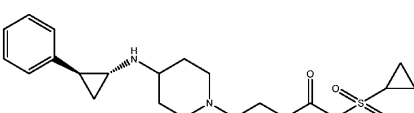
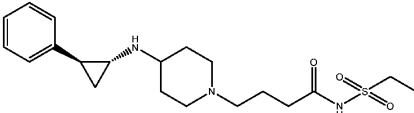
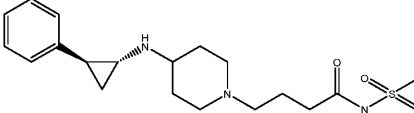
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
129	 N-methyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)methanesulfonamide	Example 39	352.1	(400 MHz, methanol- <i>d</i> ₄) δ = 7.28 - 7.20 (m, 2H), 7.16 - 7.10 (m, 1H), 7.05 (d, <i>J</i> = 8.0 Hz, 2H), 3.30 (t, <i>J</i> = 6.8 Hz, 2H), 3.02 - 2.94 (m, 2H), 2.89 (d, <i>J</i> = 7.2 Hz, 6H), 2.71 - 2.62 (m, 1H), 2.57 (t, <i>J</i> = 6.8 Hz, 2H), 2.31 (td, <i>J</i> = 3.6, 7.2 Hz, 1H), 2.10 (br t, <i>J</i> = 11.6 Hz, 2H), 1.99 - 1.84 (m, 3H), 1.54 - 1.40 (m, 2H), 1.12 - 0.99 (m, 2H).
130	 N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)cyclopropanesulfonamide	Example 38	364.1	(400 MHz, methanol- <i>d</i> ₄) δ = 7.26 - 7.21 (m, 2H), 7.16 - 7.10 (m, 1H), 7.07 - 7.03 (m, 2H), 3.28 - 3.21 (m, 2H), 2.96 (br d, <i>J</i> = 12 Hz, 2H), 2.72 - 2.62 (m, 1H), 2.60 - 2.50 (m, 3H), 2.32 (ddd, <i>J</i> = 3.6, 4.4, 7.6 Hz, 1H), 2.16 - 2.06 (m, 2H), 1.99 - 1.86 (m, 3H), 1.55 - 1.42 (m, 2H), 1.11 - 0.96 (m, 6H).
131	 1,1-dimethyl-3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)urea	Example 37	331.2	(400 MHz, Methanol- <i>d</i> ₄) δ = 7.24 (t, <i>J</i> = 7.4 Hz, 2H), 7.16 - 7.10 (m, 1H), 7.05 (d, <i>J</i> = 7.2 Hz, 2H), 3.32 - 3.28 (m, 2H), 2.30 - 2.96 (m, 2H), 2.89 (s, 6H), 2.70 - 2.62 (m, 1H), 2.49 (t, <i>J</i> = 6.8 Hz, 2H), 2.37 - 2.28 (m, 1H), 2.15 - 2.06 (m, 2H), 2.01 - 1.86 (m, 3H), 1.56 - 1.41 (m, 2H), 1.11 - 1.01 (m, 2H).
132	 N-methoxy-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide	Example 45	318.1	(400 MHz, methanol- <i>d</i> ₄) δ = 7.29 - 7.21 (m, 2H), 7.16 - 7.09 (m, 1H), 7.08 - 7.00 (m, 2H), 3.75 - 3.66 (m, 3H), 3.00 (q, <i>J</i> = 6.8 Hz, 1H), 2.94 - 2.85 (m, 2H), 2.68 - 2.59 (m, 1H), 2.36 - 2.25 (m, 2H), 2.24 - 2.14 (m, 1H), 2.01 - 1.84 (m, 3H), 1.55 - 1.40 (m, 2H), 1.29 - 1.22 (m, 3H), 1.12 - 0.97 (m, 2H).
133	 3-(4-(2-(4-(methyl((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)oxazolidin-2-one	Example 20	436.2	(400 MHz, CHLOROFORM- <i>d</i>) δ = 7.44 - 7.42 (m, 2H), 7.28 - 7.24 (m, 2H), 7.17 (m, 1H), 7.05 - 7.03 (d, <i>J</i> = 7.6 Hz, 2H), 6.93 - 6.90 (m, 2H), 4.49 - 4.45 (m, 2H), 4.17 (br t, <i>J</i> = 5.2 Hz, 2H), 4.05 - 4.01 (m, 2H), 3.17 - 3.15 (br d, <i>J</i> = 10.8 Hz, 2H), 2.90 (br s, 2H), 2.55 (br s, 1H), 2.43 (s, 3H), 2.28 - 2.26 (m, 2H), 2.08 - 1.99 (m, 2H), 1.98 - 1.87 (m, 2H), 1.86 - 1.73 (m, 2H), 1.19 - 1.18 (m, 1H), 1.07 - 1.02 (q, <i>J</i> = 6.0 Hz, 1H).

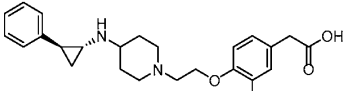
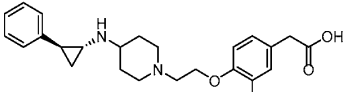
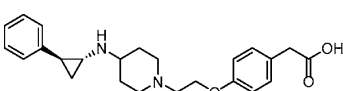
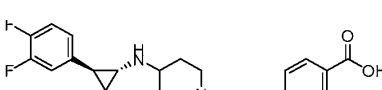
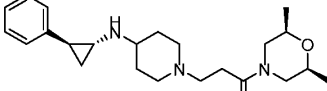
Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
134	 1-(2-(4-bromo-2-fluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 11	435.0	(400 MHz, CD ₃ Cl) δ = 7.21 - 7.04 (m, 5H), 6.95 (d, J = 7.6 Hz, 2H), 6.78 (t, J = 8.8 Hz, 1H), 4.05 (t, J = 6.0 Hz, 2H), 2.86 (d, J = 11.2 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.64 - 2.49 (m, 1H), 2.27 (m, J = 3.6, 7.2 Hz, 1H), 2.11 (t, J = 11.6 Hz, 2H), 1.91 - 1.74 (m, 3H), 1.45 - 1.29 (m, 2H), 0.99 (m, J = 4.8, 9.2 Hz, 1H), 0.92 (q, J = 6.0 Hz, 1H).
135	 N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(pyridin-3-yloxy)ethyl)piperidin-4-amine	Example 11	338.1	(400MHz, D ₂ O) δ = 8.48 - 8.47 (d, J = 2.8 Hz, 1H), 8.38 - 8.36 (d, J = 5.6 Hz, 1H), 8.14 - 8.13 (m, 1H), 7.94 - 7.93 (m, 1H), 7.29 - 7.27 (m, 2H), 7.23 - 7.21 (d, J = 7.6 Hz, 1H), 7.13 - 7.10 (m, 2H), 4.57 - 4.55 (m, 2H), 3.97 - 3.66 (m, 5H), 3.23 - 3.21 (br d, J = 8.0 Hz, 2H), 2.97 - 2.90 (m, 1H), 2.46 - 2.39 (m, 3H), 2.02 (br s, 2H), 1.48 - 1.39 (m, 2H).
136	 7-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-2H-benzo[b][1,4]oxazin-3(4H)-one	Example 11	408.1	(400 MHz, Deuterium oxide) δ 7.34 - 7.26 (m, 2H), 7.25 - 7.18 (m, 1H), 7.11 (d, J =7.6 Hz, 2H), 6.80 (d, J =8.4 Hz, 1H), 6.62 - 6.54 (m, 2H), 4.51 (d, J =1.6 Hz, 2H), 4.25 (t, J =4.4 Hz, 2H), 3.79 - 3.58 (m, 3H), 3.56 - 3.45 (m, 2H), 3.24 - 3.06 (m, 2H), 2.94 - 2.90 (m, 1H), 2.48 - 2.33 (m, 3H), 2.06 - 1.90 (m, 2H), 1.49 - 1.36 (m, 2H)
137	 6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzo[d]oxazol-2(3H)-one	Example 11	394.1	(400 MHz, Deuterium oxide) δ 7.37 - 7.18 (m, 3H), 7.12 (d, J =7.6 Hz, 2H), 6.96 (d, J =8.4 Hz, 1H), 6.87 (s, 1H), 6.76 (d, J =8.4 Hz, 1H), 4.32 - 4.24 (m, 2H), 3.92 - 3.63 (m, 3H), 3.58 - 3.49 (m, 2H), 3.23 - 3.12 (m, 2H), 3.03 - 2.86 (m, 1H), 2.55 - 2.32 (m, 3H), 2.06 - 1.92 (m, 2H), 1.56 - 1.34 (m, 2H)
138	 1-(2-((5-methylthiazol-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine	Example 36	358.2	(400 MHz, D ₂ O) δ = 7.32 - 7.29 (m, 2H), 7.25 - 7.21 (m, 1H), 7.14 - 7.12 (m, 2H), 6.94 (s, 1H), 4.75 (m, 2H), 3.78 - 3.66 (m, 5H), 3.19 (br s, 2H), 2.95 - 2.93 (m, 1H), 2.47 - 2.40 (m, 3H), 2.28 (s, 3H), 2.06 (br s, 2H), 1.49 - 1.40 (m, 2H)
139	 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanoic acid	Example 48	289.1	(400 MHz, DEUTERIUM OXIDE) δ = 7.40 - 7.18 (m, 3H), 7.16 - 7.11 (m, 2H), 3.74 - 3.57 (m, 3H), 3.38 (br t, J = 6.4 Hz, 2H), 3.19 - 3.01 (m, 2H), 2.93 (td, J = 4.4, 7.7 Hz, 1H), 2.87 - 2.74 (m, 2H), 2.50 - 2.25 (m, 3H), 1.94 (br s, 2H), 1.51 - 1.35 (m, 2H)

Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
140	 3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)isonicotinic acid	Example 36	382.1	(400 MHz, D ₂ O) δ = 8.60 (s, 1H), 8.52 - 8.50 (d, <i>J</i> = 5.8 Hz, 1H), 7.90 - 7.88 (d, <i>J</i> = 5.6 Hz, 1H), 7.38 - 7.35 (m, 2H), 7.31 - 7.29 (m, 1H), 7.20 - 7.18 (d, <i>J</i> = 7.2 Hz, 2H), 4.66 - 4.64 (m, 2H), 3.85 - 3.83 (m, 2H), 3.72 (m, 3H), 3.29 - 3.26 (m, 2H), 3.02 - 3.00 (m, 1H), 2.53 - 2.47 (m, 3H), 2.06 (m, 2H), 1.55 - 1.46 (m, 2H).
141	 2-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)isonicotinic acid	Example 36	381.1	(400 MHz, Deuterium oxide) δ 7.90 (d, <i>J</i> =6.4 Hz, 1H), 7.42 (s, 1H), 7.37 - 7.20 (m, 4H), 7.14 (d, <i>J</i> =7.2 Hz, 2H), 3.86 (t, <i>J</i> =6.2 Hz, 2H), 3.80 - 3.64 (m, 3H), 3.47 (t, <i>J</i> =6.2 Hz, 2H), 3.26 - 3.10 (m, 2H), 3.00 - 2.92 (m, 1H), 2.51 - 2.37 (m, 3H), 2.10 - 1.92 (m, 2H), 1.55 - 1.39 (m, 2H).
142	 3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)isonicotinic acid	Example 36	381.1	(400 MHz, Deuterium oxide) δ 8.17 (s, 1H), 8.11 (d, <i>J</i> =5.6 Hz, 1H), 7.90 (d, <i>J</i> =5.6 Hz, 1H), 7.26 - 7.19 (m, 2H), 7.18 - 7.11 (m, 1H), 7.08 - 7.02 (m, 2H), 3.79 - 3.56 (m, 5H), 3.40 - 3.32 (m, 2H), 3.22 - 3.00 (m, 2H), 2.92 - 2.82 (m, 1H), 2.44 - 2.22 (m, 3H), 2.02 - 1.82 (m, 2H), 1.49 - 1.30 (m, 2H).
143	 N-(methylsulfonyl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide	Example 48	366.1	¹ H NMR 500 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 12.03 (bs, 1H), 10.72 (bs, 1H), 9.97 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.57-3.51 (m, 3H), 3.27 (m, 2H), 3.26 (s, 3H), 3.02 (bs, 2H), 2.07 (m, 1H), 2.89 (t, <i>J</i> = 7.3 Hz, 2H), 2.57 (m, 1H), 2.29 (bs, 2H), 2.07 (m, 2H), 1.59 (m, 1H), 1.31-1.27 (m, 1H).
144	 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-(piperazin-1-yl)propan-1-one	Example 48	357.3	¹ H NMR 500 MHz, DMSO- <i>d</i> ₆ , δ (ppm): 10.98 and 10.71 (two bs, 1H, mixture of rotamers), 10.25 and 10.06 (2 bs, 2H, mixture of rotamers), 9.52 and 9.44 (2 bs, 2H, mixture of rotamers), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.70 (bs, 4H), 3.60 (bs, 2H), 3.45 (bs, 1H), 3.24 (bt, 2H), 3.15 (bs, 2H), 3.05-3.01 (m, 4H), 2.95-2.93 (m, 3H), 2.67 and 2.58 (two m, 1H, mixture of rotamers), 2.32-2.24 (m, 2H), 2.08 (bs, 2H), 1.67 and 1.60-1.57 (bs and m, 1H, mixture of rotamers), 1.31-1.27 (m, 1H).

Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
145	 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-N-(phenylsulfonyl)propanamide	Example 48	428.2	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 12.51 (bs, 1H), 10.59 (bs, 1H), 9.96 (bs, 2H), 7.94-7.92 (m, 2H), 7.72-7.69 (m, 1H), 7.64-7.61 (m, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.42-3.40 (m, 3H), 3.16 (bt, 2H), 2.96-2.93 (m, 3H), 2.85 (t, <i>J</i> = 7.1 Hz, 2H), 2.56 (m, 1H), 2.23 (bs, 2H), 2.02 (m, 2H), 1.59-1.55 (m, 1H), 1.30-1.26 (m, 1H).
146	 1-(4-methylpiperazin-1-yl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one	Example 48	371.3	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 11.42 (bs, 1H), 11.03 and 10.76 (2 bs, 1H, mixture of rotamers), 10.05 (2 bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 4.40 (bs, 1H), 4.03 (bs, 1H), 3.60-3.53 (m, 3H), 3.45 (bs, 1H), 3.43 (bs, 1H), 3.24 (bt, 2H), 3.04 (bs, 4H), 2.96 (bs, 4H), 2.75 (s, 3H), 2.67 and 2.59 (two m, 1H, mixture of rotamers), 2.33 (bs, 1H), 2.30 (bs, 1H), 2.23 (bs, 1H), 2.08 (m, 2H), 1.66 and 1.61-1.57 (bs and m, 1H, mixture of rotamers), 1.31-1.27 (m, 1H).
147	 N-(ethylsulfonyl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide	Example 48	380.2	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 11.93 (bs, 1H), 10.76 (bs, 1H), 10.02 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.54-3.50 (m, 3H), 3.36 (q, <i>J</i> = 7.4 Hz, 2H), 3.27 (bt, 2H), 3.01-2.90 (m, 5H), 2.67 and 2.57 (two m, 1H, rotamers), 2.29 (bs, 2H), 2.08 (m, 2H), 1.60 (m, 1H), 1.31-1.27 (m, 1H), 1.23 (t, <i>J</i> = 7.4 Hz, 3H).
148	 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-thiomorpholinopropan-1-one	Example 48	374.7	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 10.63 and 10.47 (two bs, 1H, mixture of rotamers), 10.15 and 10.00 (two bs, 2H, mixture of rotamers), 7.33-7.30 (m, 2H), 7.24-7.18 (m, 3H), 3.73-3.68 (m, 4H), 3.61 (bt, 2H), 3.45 (bs, 1H), 3.24 (bt, 2H), 3.06-2.93 (m, 3H), 2.89 (t, <i>J</i> = 7.7 Hz, 2H), 2.66-2.64 (m, 2H), 2.59-2.53 (m, 3H), 2.30 and 2.21 (two bs, 2H), 2.11-2.01 (m, 2H), 1.66 and 1.60-1.56 (bs and m, 1H, mixture of rotamers), 1.31-1.27 (m, 1H).

Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
149	 1-(4-methylpiperazin-1-yl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butan-1-one	Example 48	385.3	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 11.33 and 11.19 (two bs, 1H, mixture of rotamers), 11.00 and 10.70 (two bs, 1H, mixture of rotamers), 10.22 and 10.03 (two bs, 2H, mixture of rotamers), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 4.42 (bd, 1H), 4.02 (bd, 1H), 3.57-3.38 (m, 6H), 3.08-2.91 (m, 8H), 2.74 (s, 3H), 2.66 and 2.59-2.55 (two m, 1H, mixture of rotamers), 2.32 (bs, 1H), 2.29 (bs, 1H), 2.30 (bs, 1H), 2.24-2.23 (m, 1H), 2.15-2.05 (m, 2H), 1.96-1.89 (m, 2H), 1.67 and 1.61-1.57 (two m, 1H, mixture of rotamers), 1.30-1.26 (m, 1H). MS: 384.6 (calcd.), 385.3 (M+H ⁺ , found).
150	 4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-(piperazin-1-yl)butan-1-one	Example 48	371.3	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 11.00 and 10.69 (two bs, 1H, mixture of rotamers), 10.04 (bs, 2H), 9.48 and 9.41 (two bs, 2H, mixture of rotamers), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.69-3.67 (m, 4H), 3.57 (bs, 2H), 3.46 (bs, 1H), 3.12 (bs, 2H), 3.02-2.97 (7H), 2.69-2.64 and 2.60-2.56 (two m, 1H, mixture of rotamers), 2.32 (bs, 1H), 2.30 (bs, 1H), 2.23 (bs, 1H), 2.14-2.05 (m, 1H), 2.14-2.05 (m, 2H), 1.96-1.88 (m, 2H), 1.67 and 1.61-1.57 (two m, 1H, mixture of rotamers), 1.30-1.26 (m, 1H).
151	 1-morpholino-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butan-1-one	Example 48	372.3	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 10.78 and 10.52 (two bs, 1H, mixture of rotamers), 10.14 and 10.00 (two bs, 2H, mixture of rotamers), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.58-3.53 (m, 6H), 3.44-3.41 (m, 4H), 3.11-3.07 and 3.02-2.94 (two m, 5H, mixture of rotamers), 2.67-2.63 and 2.59-2.55 (two m, 1H, mixture of rotamers), 2.43 (t, J = 7.1 Hz, 2H), 2.32 (bs, 1H), 2.29 (bs, 1H), 2.23-2.20 (m, 1H), 2.13-2.03 (m, 2H), 1.94-1.88 (m, 2H), 1.68-1.64 and 1.61-1.57 (two m, 1H, mixture of rotamers), 1.33-1.27 (m, 1H).

Ex. #	Structure	Method	LCMS [M+] Observed	¹ H NMR
152	 4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-N-(phenylsulfonyl)butanamide	Example 48	442.2	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 12.26 (bs, 1H), 10.50 (bs, 1H), 9.97 (bs, 2H), 7.93-7.91 (m, 2H), 7.74-7.70 (m, 1H), 7.65-7.61 (m, 2H), 7.32-7.29 (m, 2H), 7.24-7.19 (m, 3H), 3.50 (bs, 2H), 3.44 (bs, 1H), 2.96-2.91 (m, 4H), 2.56 (bs, 1H), 2.35 (t, <i>J</i> = 7.2 Hz, 2H), 2.25 (bs, 2H), 2.05 (m, 3H), 1.85-1.79 (m, 2H), 1.58 (bs, 1H), 1.30-1.26 (m, 1H).
153	 4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanoic acid	Example 48	303.2	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 12.29 (bs, 1H), 10.88 and 10.56 (two bs, 1H), 10.05 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.56 (bs, 2H), 3.46 (m, 1H), 3.00-2.96 (m, 5H), 2.58 (m, 1H), 2.34-2.22 (m, 4H), 2.08 (m, 2H), 1.94-1.66 (m, 2H), 1.61-1.57 (m, 1H), 1.31-1.27 (m, 1H).
154	 N-(cyclopropylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide	Example 48	406.6	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 11.77 (bs, 1H), 10.62 (bs, 1H), 10.01 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.56 (bs, 2H), 3.46 (bs, 1H), 2.99-2.91 (m, 6H), 2.57 (bs, 1H), 2.40 (t, <i>J</i> = 7.2 Hz, 2H), 2.31 (bs, 1H), 2.29 (bs, 1H), 2.08 (m, 2H), 1.97-1.91 (m, 2H), 1.59 (bs, 1H), 1.31-1.27 (m, 1H), 1.10-1.07 (m, 4H). MS: 405.6 (calcd.), 406.6 (M+H ⁺ , found).
155	 N-(ethylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide	Example 48	394.7	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 11.70 (bs, 1H), 10.58 (bs, 1H), 9.99 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 3.57 (bs, 2H), 3.46 (bs, 1H), 3.35 (q, <i>J</i> = 7.4 Hz, 2H), 2.97 (bs, 4H), 2.57 (m, 1H), 2.41 (t, <i>J</i> = 7.1 Hz, 2H), 2.31 (bs, 1H), 2.28 (bs, 1H), 2.21 (bs, 1H), 2.07 (m, 2H), 1.96-1.90 (m, 2H), 1.60-1.56 (m, 1H), 1.31-1.27 (m, 1H), 1.21 (t, <i>J</i> = 7.3 Hz, 3H).
156	 N-(methylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide	Example 48	380.2	¹ H NMR 500 MHz, DMSO-d ₆ , δ (ppm): 11.83 (bs, 1H), 10.62 (bs, 1H), 10.02 (bs, 2H), 7.33-7.30 (m, 2H), 7.25-7.19 (m, 3H), 3.57 (bs, 2H), 3.51-3.47 (m, 1H), 3.25 (s, 3H), 2.98 (bs, 4H), 2.68 and 2.58 (m and bs, 1H, mixture of rotamers), 2.43 (t, <i>J</i> = 7.1 Hz, 2H), 2.33 (bs, 1H), 2.30 (bs, 1H), 2.23 (bs, 1H), 2.09 (bs, 2H), 1.97-1.91 (m, 2H), 1.62-1.58 (m, 1H), 1.32-1.28 (m, 1H).

Ex. #	Structure	Method	LCMS [M+1] Observed	¹ H NMR
157	 2-(3-chloro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid	Example 43	429.7	¹ H NMR 500 MHz, DMSO ₆ , δ (ppm): 12.36 (bs, 1H), 10.95 (bs, 1H), 10.00 (bs, 2H), 7.37 (d, <i>J</i> = 2.4 Hz, 1H), 7.32-7.29 (m, 2H), 7.24-7.14 (m, 5H), 4.48 (bt, 2H), 3.72 (bs, 2H), 3.55 (s, 2H), 3.51 (bs, 2H), 3.47 (bs, 1H), 3.19 (bs, 2H), 2.97 (bs, 1H), 2.57 (m, 1H), 2.33 (bs, 2H), 2.11 (bs, 2H), 1.61-1.57 (m, 1H), 1.31-1.27 (m, 1H). MS: 429.0 (calcd.).
158	 2-(3-fluoro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid	Example 43	413.7	¹ H NMR 500 MHz, DMSO ₆ , δ (ppm): 12.36 (bs, 1H), 11.18 and 10.93 (two bs, 1H), 10.04 (bs, 2H), 7.32-7.29 (m, 2H), 7.21-7.15 (m, 5H), 7.05 (m, 1H), 4.47 (bt, 2H), 3.68 (bs, 1H), 3.67 (bs, 1H), 3.54 (s, 2H), 3.59 (bs, 3H), 3.15 (bs, 2H), 2.96 (bs, 1H), 2.58 (m, 1H), 2.33 (bs, 2H), 2.10 (bs, 2H), 1.61-1.57 (m, 1H), 1.31-1.26 (m, 1H). MS: 412.5 (calcd.).
159	 2-(3-methyl-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid	Example 43	409.7	¹ H NMR 500 MHz, DMSO ₆ , δ (ppm): 12.20 (bs, 1H), 11.12 and 10.90 (two bs, 1H), 9.98 (bs, 2H), 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 7.06-7.05 (m, 2H), 6.90-6.89 (m, 1H), 4.37 (bt, 2H), 3.67 (bs, 1H), 3.66 (bs, 1H), 3.48 (bs, 2H), 3.46 (s, 2H), 3.17 (bs, 2H), 2.96 (bs, 1H), 2.64 and 2.56 (two m, 1H, rotamers), 2.33 (bs, 2H), 2.16 (s, 3H), 2.11 (bs, 2H), 1.60-1.56 (m, 1H), 1.31-1.27 (m, 1H).
160	 4-(2-(4-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)piperidin-1-yl)ethoxy)benzoic acid	Example 43	417.6	¹ H NMR 500 MHz, DMSO ₆ , δ (ppm): 12.69 (bs, 1H), 11.21 and 10.96 (two bs, 1H), 10.12 (bs, 2H), 7.93 (d, <i>J</i> = 8.9 Hz, 2H), 7.40-7.29 (m, 2H), 7.12-7.08 (m, 3H), 4.49 (bt, 2H), 3.69 (bs, 1H), 3.67 (bs, 1H), 3.50-3.43 (m, 3H), 3.15 (bs, 2H), 3.01 (bs, 1H), 2.61 (m, 1H), 2.34 (bs, 1H), 2.32 (bs, 1H), 2.11 (bs, 2H), 1.64-1.60 (m, 1H), 1.35-1.31 (m, 1H).
161	 1-(<i>cis</i>-2,6-dimethylmorpholino)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one	Example 43	386.7	¹ H NMR: 500 MHz, D ₂ O, δ (ppm): 7.44-7.40 (m, 2H), 7.37-7.33 (m, 1H), 7.25-7.23 (m, 2H), 4.32-4.29 (m, 1H), 3.82-3.66 (m, 7H), 3.49 (bt, 2H), 3.18 (bs, 2H), 3.07-3.01 (m, 2H), 2.99-2.91 (m, 2H), 2.58-2.49 (m, 4H), 2.06 (bs, 2H), 1.60-1.50 (m, 2H), 1.27-1.21 (m, 6H, mixture of rotamers).

[0510] The compounds of the present invention have two or more chiral centers and are synthesized as stereoisomeric mixtures, isomers of identical constitution that differ in the arrangement of their atoms in space. The compounds may be used as mixtures or the individual components/isomers may be separated using commercially available reagents and conventional methods for isolation of stereoisomers and enantiomers well-known to those skilled in the art, *e.g.*, using CHIRALPAK® (Sigma-Aldrich) or CHIRALCEL® (Diacel Corp) chiral chromatographic HPLC columns according to the manufacturer's instructions. Alternatively, compounds of the present invention may be synthesized using optically pure, chiral reagents and intermediates to prepare individual isomers or enantiomers as described, for example, in Examples 7 & 8. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention.

EXAMPLE A

[0511] This Example illustrates that exemplary compounds of the present invention inhibit LSD1 enzymatic activity.

[0512] Ten-point dose-response curves for compounds shown in Table 3 were determined using a fluorescence coupling enzymatic assay using purified N-terminal truncated human LSD1 enzyme (aa 151-852; Genbank Accession No NM015013) containing an N-terminal His-Tag (Reaction Biology Corp). In this assay, hydrogen peroxide is produced by the LSD1 FAD-dependent demethylase activity using a horseradish peroxidase/Amplex Red coupling reaction resulting in the production of highly fluorescent compound, Resorufin, which is detected at 590 nM.

[0513] Briefly, compounds of the present invention were solubilized in DMSO and a series of 10, three-fold serial dilutions were made for each compound in 15% DMSO. The initial starting concentration for the serial dilutions of each compound was 10 μ M. Control samples lacking compound, LSD1 enzyme or various reaction components also were prepared and processed in parallel with compound test samples.

[0514] An aliquot of each serial dilution of test compound was added to a 96 well plate containing 50 nM purified N-truncated LSD1 enzyme (RBC Cat# PDM-11-350), 50 mM Tris-HCl, pH 7.5, 0.05% CHAPS and 1% DMSO in a 10 microliter reaction volume. The plate was pre-incubated at room temperature for 30 min to which 10 μ M of histone 3.3 peptide (aa 1-21) was added to initiate the enzymatic reaction. The reaction mixture was incubated at room temperature for one hour. After one hour, 10 μ l of a detection mixture of horseradish peroxidase (Sigma Cat #P8375) and Amplex Red (Invitrogen A36006) was added and kinetic

measurements were read at 5 minute intervals for a period of 30 minutes using an Envision Multiplate Reader (PerkinElmer; excitation at 535 nM and emission read at 590 nM). The IC₅₀ value for each compound was determined from each 10-point dose-response curve using GraphPad Prism 4 software with a sigmoidal dose response. The results for exemplary compounds of Formula (I) and Formula (II) are shown in Table 3.

Table 3
Inhibition of LSD1 Activity by Exemplary Compounds of Formula (I)

Example Number	IC₅₀ (nM)	Example Number	IC₅₀ (nM)	Example Number	IC₅₀ (nM)
1	36	55	4	109	24
2	110	56	5	110	9
3	33	57	2	111	7
4	47	58	3	112	35
5	17	59	8	113	9
6	28	60	1	114	12
7	15	61	12	115	14
8	13	62	8	116	38
9	110	63	14	117	17
10	8	64	0.9	118	709
11	10	65	8	119	38
12	5	66	4	120	18
13	25	67	8	121	24
14	16	68	6	122	31
15	11	69	33	123	8
16	7	70	8	124	71
17	4	71	31	125	19
18	7	72	17	126	19
19	3	73	5	127	286
20	5	74	4	128	2
21	5	75	20	129	10
22	5	76	11	130	14
23	4	77	10	131	19
24	3	78	7	132	232
25	46	79	31	133	15
26	50	80	22	134	26
27	116	81	23	135	25
28	8	82	39	136	11
29	4	83	76	137	7
30	14	84	19	138	18
31	87	85	6	139	277
32	22	86	7	140	154
33	< 1	87	22	141	11
34	3	88	25	142	127
35	21	89	4	143	221

Example Number	IC ₅₀ (nM)	Example Number	IC ₅₀ (nM)	Example Number	IC ₅₀ (nM)
36	33	90	20	144	9
37	108	91	4	145	21
38	23	92	123	146	8
39	25	93	46	147	148
40	11	94	17	148	15
41	15	95	5	149	14
42	10	96	624	150	5
43	17	97	57	151	9
44	9	98	13	152	20
45	225	99	349	153	192
46	58	100	39	154	440
47	74	101	319	155	134
48	10	102	14	156	231
49	21	103	19	157	3
50	3	104	5	158	8
51	6	105	6	159	20
52	6	106	14	160	15
53	12	107	27	161	17
54	7	108	11		

EXAMPLE B

[0515] This Example illustrates that exemplary compounds of the present invention inhibit the growth of tumor cell lines that express LSD1.

[0516] The MV4-11 cell line cell line was established from the blast cells of a 10-year-old male with biphenotypic B-myelomonocytic leukemia. This cell line expresses a leukemic fusion protein (MLL-AF9+), LSD1 and has been shown to be sensitive to inhibitors of LSD1.

[0517] Inhibition of LSD1-mediated cellular proliferation by compounds of Formula (I) or Formula (II) was measured in a CellTiter Glo luminescence assay (Promega Corp), which determines the number of viable cells by quantitating the amount of ATP, using a BMG LabTech CLARIOStar instrument in accordance with the manufacturer's instructions. Briefly, MV4-11 cells were plated at a density of 1000 cells/90μl/well in 96 well culture plates and cultured in IMDM medium (Gibco) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin and 1% streptomycin at 37°C. A series of 3-fold serial dilutions of each test compound of Formula (I) was prepared in IMDM medium lacking FBS and added to the cells at final concentrations ranging from 1μM to 0.01 nM. Control samples lacking test compound or cells were processed in parallel. The plates were incubated at 37°C for four days and thereafter 50 μl fresh medium containing the same concentration of test compound was added. The plates were

incubated for an additional three days (Day 7). A baseline measurement, as described below, was taken for a time zero point at Day 0.

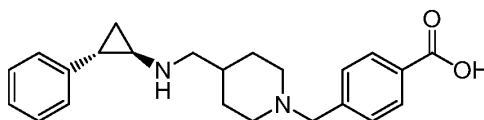
[0518] At Day 7, the supernatant was removed by aspiration and the plate was allowed to equilibrate to room temperature (~15 min). The cells were lysed using 45µl (30 µl for Day 0) of Cell Titer Glo reagent (Promega Corp). The plates were shaken for two minutes and incubated at room temperature for 30 minutes. The degree of inhibition of cell viability was determined using a spectrophotometric readout by measuring the luminescence at 340 nm and the EC₅₀ concentration for each compound was calculated using Graph Pad Prism 4 software. The results are shown in Table 4. Key: N/D = not determined.

Table 4
Inhibition of LSD1-mediated Cell Proliferation by Exemplary Compounds
of Formula (I) and Formula (II)

Example Number	IC ₅₀ (nM)	Example Number	IC ₅₀ (nM)	Example Number	IC ₅₀ (nM)
1	13	55	< 1	109	< 1
2	34	56	< 1	110	5
3	2	57	< 1	111	13
4	14	58	< 1	112	< 1
5	< 1	59	< 1	113	3
6	14	60	< 1	114	3
7	2	61	7	115	1
8	2	62	4	116	6
9	3	63	< 1	117	2
10	< 1	64	11	118	23
11	< 1	65	7	119	5
12	< 1	66	9	120	3
13	2	67	4	121	6
14	2	68	10	122	5
15	< 1	69	28	123	< 1
16	33	70	4	124	7
17	8	71	2	125	29
18	< 1	72	10	126	4
19	1	73	3	127	530
20	< 1	74	3	128	< 1
21	< 1	75	10	129	< 1
22	< 1	76	< 1	130	< 1
23	< 1	77	< 1	131	2
24	< 1	78	117	132	7
25	< 1	79	< 1	133	61
26	< 1	80	< 1	134	3
27	< 1	81	< 1	135	1
28	< 1	82	< 1	136	< 1

Example Number	IC ₅₀ (nM)	Example Number	IC ₅₀ (nM)	Example Number	IC ₅₀ (nM)
29	< 1	83	5	137	< 1
30	< 1	84	1	138	3
31	10	85	< 1	139	37
32	33	86	5	140	30
33	< 1	87	22	141	60
34	< 1	88	5	142	38
35	3	89	< 1	143	10
36	28	90	34	144	< 1
37	2	91	< 1	145	3
38	< 1	92	9	146	< 1
39	5	93	24	147	9
40	< 1	94	< 1	148	3
41	< 1	95	< 1	149	< 1
42	28	96	67	150	< 1
43	10	97	< 1	151	2
44	1	98	>1000	152	6
45	56	99	28	153	13
46	10	100	< 1	154	1
47	885	101	3	155	1
48	3	102	N/D	156	8
49	14	103	< 1	157	28
50	< 1	104	< 1	158	29
51	< 1	105	< 1	159	10
52	< 1	106	10	160	10
53	< 1	107	< 1	161	1
54	< 1	108	< 1		

[0519] As evidenced in Examples A & B, many of the compounds of formula (I) and formula (II) of the present invention demonstrate at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold or as much as at least 50-fold greater potency than the LSD1 inhibitor GSK2879552



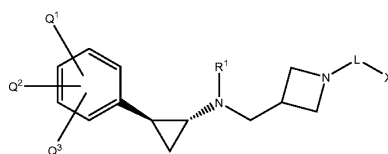
presently in Phase I clinical trials (ClinicalTrials.gov Identifier: NCT02177812).

[0520] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be

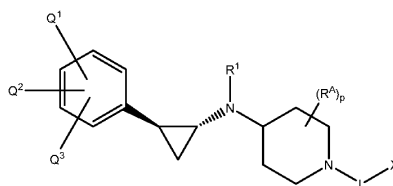
applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WE CLAIM:

1. A compound of formula (I) or formula (II):



Formula (I)



Formula (II)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is hydrogen, C₁-C₄ alkyl or C₁-C₄ acyl;

L is $-(CH_2)_s-CR^2R^3-(CH_2)_n-$;

R^2 and R^3 are each independently hydrogen, C₁-C₄ alkyl, $-OR^4$ or aralkyl;

each R^4 is independently hydrogen or C₁-C₄ alkyl;

X is $-W-R^5$ or $Y-R^6$;

W is $-NR^4-$ or $-O-$;

Y is $-C(O)-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^4SO_2-$, $-SO_2NR^4-$ or $-NR^4C(O)-$;

R^5 is acyl, C₁-C₄ alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally independently substituted with one or more R^8 ;

R^6 is C₁-C₆ alkyl, aryl, $-NR^4R^7$ or heterocyclyl optionally independently substituted on one or more carbon atoms with C₁-C₆ alkyl, halogen, cyano, haloalkyl or optionally independently substituted on one or more nitrogen atom with $-C(O)C_1-C_6$ alkyl; $-C(O)OC_1-C_6$ alkyl; $-C(O)NR^4C_1-C_6$ alkyl, or $-S(O)_2NR^4C_1-C_6$ alkyl;

R⁷ is hydroxyl, alkoxy, -SO₂C₁-C₆alkyl; -SO₂cycloalkyl, or -SO₂aryl, wherein the cycloalkyl or aryl of each of the -SO₂cycloalkyl and -SO₂aryl is optionally independently substituted with one or more R⁸;

each R⁸ is halogen, hydroxyl, amino, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, haloalkyl, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, -(CH₂)_nCOOR⁴, -(CH₂)_nC(O)NR⁴OC₁-C₆alkyl; -(CH₂)_nC(O)NR⁴SO₂C₁-C₆alkyl, -(CH₂)_nC(O)NR⁴SO₂cycloalkyl, -(CH₂)_nC(O)NR⁴SO₂aryl, -C₂-C₆ alkenylC(O)OR⁴, -C₂-C₆ alkenylC(O)NR⁴SO₂ C₁-C₄ alkyl, or -C₂-C₆ alkenylC(O) NR⁴SO₂aryl, wherein each of the cycloalkyl, aryl, heteroaryl, heterocyclyl is optionally independently substituted with one or more C₁-C₃ alkyl or -CH₂NR⁴SO₂aryl.

m is 0 or 1;

s is 0 or 1;

each n is 0, 1, or 2;

each p is 0, 1 or 2;

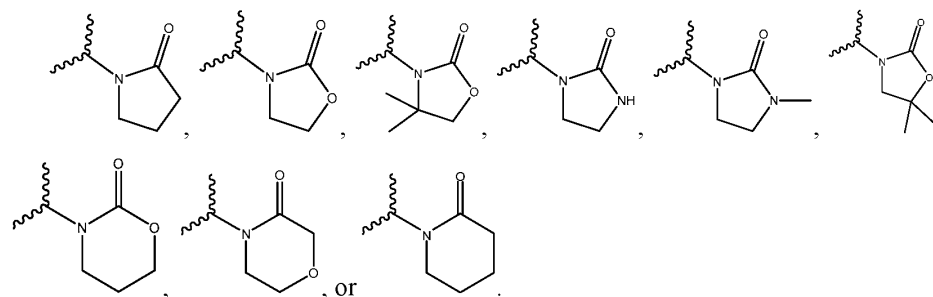
each R^A group is independently oxo or C₁-C₃ alkyl, or two R^A groups on different ring atoms together form a C₁-C₃ bridge in which one of the bridge carbons is optionally replaced with -NH-; and

each Q¹, Q² and Q³ is independently hydrogen, halogen, haloalkyl, C₁-C₄-alkyl, or C₁-C₄-alkoxy.

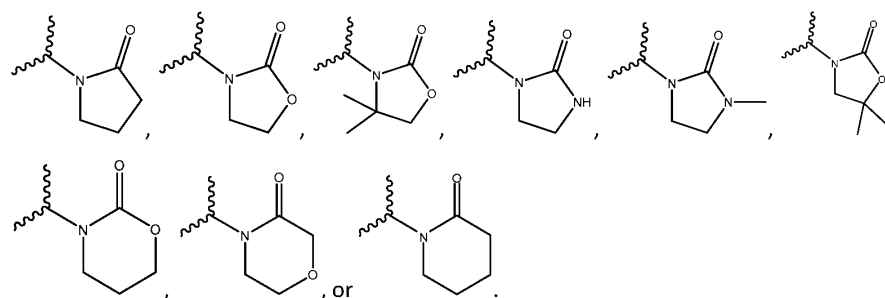
2. The compound of claim 1, wherein W is -O- and s is 1 and m is 0.
3. The compound of claim 2, wherein R⁵ is aryl optionally independently substituted with one or more R⁸.
4. The compound of claim 3, wherein the aryl is phenyl optionally independently substituted with one or more R⁸.
5. The compound of claim 4, wherein R⁸ is heterocyclyl optionally independently substituted one or more C₁-C₃ alkyl or C₁-C₄acyl.
6. The compound of claim 5, wherein the heterocyclyl is azetidiny, pyrrolidiny, pyrazolidiny, piperidiny, piperaziny, 4-methyl-piperaziny, 4-acyl-piperaziny,

tetrahydropyranyl, 1,3-dioxolanyl, 1,4-dioxanyl, morpholiny, dimethyl-morpholiny, thiomorpholiny, 1,4-dithianyl, or 1,3,5-trithianyl.

7. The compound of claim 5, wherein the heterocyclyl is:



8. The compound of claim 4, wherein R^8 is halogen, alkyl, $-(CH_2)_nCOOR^4$, $-(CH_2)_nC(O)NR^4SO_2C_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4OC_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4SO_2cycloalkyl$, $-(CH_2)_nC(O)NR^4SO_2aryl$, $-CH=CHC(O)OR^4$, $-CH=CHC(O)NR^4SO_2C_1-C_4alkyl$, or $-CH=CHC(O)NR^4SO_2aryl$.
9. The compound of claim 2, wherein R^5 is heteroaryl optionally independently substituted with one or more R^8 .
10. The compound of claim 9, wherein the heteroaryl is pyridyl, 6-methyl-pyridyl, 4-carboxy-pyridyl, dihydroquinolinone, indolinone, quinazolinyl, quinoliny, pyrimidinyl, 2-methyl-pyrimidinyl, pyridazinyl, 6-methyl-pyridiazinyl, pyrazolyl, 1-methyl-pyrazolyl, 5-methyl-pyrazolyl, 1,3-dimethyl-pyrazolyl, thiazolyl, 5-methyl-thiazolyl, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, thiadiazolyl or 5-methyl-thiadiazolyl.
11. The compound of claim 9, wherein the heteroaryl is pyridyl optionally independently substituted with one or more R^8 .
12. The compound of claim 11, wherein R^8 is heterocyclyl optionally independently substituted one or more C_1-C_3 alkyl.
13. The compound of claim 12, wherein the heterocyclyl is azetidiny, pyrrolidiny, pyrazolidiny, piperidiny, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, tetrahydropyranyl, 1,3-dioxolanyl, 1,4-dioxanyl, morpholiny, dimethyl-morpholiny, thiomorpholiny, 1,4-dithianyl, or 1,3,5-trithianyl.
14. The compound of claim 12, wherein the heterocyclyl is:



15. The compound of claim 9, wherein R^8 is halogen, alkyl, $-(CH_2)_nCOOR^4$, $-(CH_2)_nC(O)NR^4OC_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4SO_2C_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4SO_2cycloalkyl$, $-(CH_2)_nC(O)NR^4SO_2aryl$, $-CH=CHC(O)OR^4$, $-CH=CHC(O)NR^4SO_2C_1-C_4alkyl$, or $-CH=CHC(O)NR^4SO_2aryl$.
16. The compound of formula (II) of claim 2, wherein R^A is oxo and n is 1 or 2.
17. The compound of formula (II) of claim 2, wherein two R^A groups on different ring atoms together form a C_1-C_3 bridge in which one of the bridge carbons is optionally replaced with $-NH-$.
18. The compound of claim 2, wherein the compound is
 - 1-phenoxy-3-[4-[[trans-2-phenylcyclopropyl] amino]-1-piperidyl] propan-2-ol;
 - 1-(2-methoxy-3-phenoxy-propyl)-N-[trans-2-phenylcyclopropyl]piperidin-4-amine;
 - 2-methyl-1-phenoxy-3-(4-(((trans)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol;
 - 1-phenoxy-3-[3-[[[(trans)-2-phenylcyclopropyl]amino]methyl]azetidin-1-yl]propan-2-ol;
 - (R)-1-phenoxy-3-(4-(((1S,2R)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol;
 - (S)-1-phenoxy-3-(4-(((1S,2R)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-2-ol;
 - 1-phenoxy-3-[(1R,5S)-6-[[[(trans)-2-phenylcyclopropyl]amino]-3-azabicyclo[3.1.1]heptan-3-yl]propan-2-ol;
 - (trans)-N-[[1-(2-phenoxyethyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine;
 - (trans)-N-[[1-(3-phenoxypropyl)azetidin-3-yl]methyl]-2-phenyl-cyclopropanamine;
 - 1-[2-(4-bromophenoxy)ethyl]-N-[(1R,2S)-2-phenylcyclopropyl]piperidin-4-amine;

1-(3-Phenoxypropyl)-N-((trans)-2-phenylcyclopropyl)piperidin-4-amine;

1-(2-Phenoxyethyl)-N-((trans)-2-phenylcyclopropyl)piperidin-4-amine;

2-(4-(2-(4-(((1R,2S)-2-Phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;

N-(Methylsulfonyl)-2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide;

2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-N-(phenylsulfonyl)acetamide;

N,N-Dimethyl-2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide;

N-methoxy-2-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetamide;

1-[2-(4-morpholinophenoxy)ethyl]-N-[(1R,2S)-2-phenylcyclopropyl]piperidin-4-amine;

1-(2-(4-(4-methylpiperazin-1-yl)phenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)oxazolidin-2-one;

1-methyl-3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)imidazolidin-2-one;

3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;

4-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)morpholin-3-one;

1-(4-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)piperazin-1-yl)ethan-1-one;

1-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)pyrrolidin-2-one;

1-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)piperidin-2-one;

N-(((1R,2S)-2-phenylcyclopropyl)-1-(2-(4-(piperidin-1-yl)phenoxy)ethyl)piperidin-4-amine;

2-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acetic acid;

4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)benzoic acid;

(*E*)-3-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylic acid;

2-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acetic acid;

4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)benzoic acid;

(*E*)-3-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylic acid;

(1R,2S)-N-((1-(2-(4-bromophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;

1-(2-(2,4-dichlorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

(1R,2S)-N-((1-(2-(2,4-dichlorophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;

1-(2-(2,4-difluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

(1R,2S)-N-((1-(2-(2,4-difluorophenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;

(*E*)-3-(4-(2-hydroxy-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)-N-(methylsulfonyl)acrylamide;

1-(2-((2-methylpyridin-4-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

(1R,2S)-2-phenyl-N-((1-(2-(p-tolylloxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine;

(1R,2S)-2-phenyl-N-((1-(2-(pyridin-2-yloxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine;

4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzoic acid;

N-(cyclopropylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide;

4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-N-(phenylsulfonyl)benzamide;

(E)-N-(methylsulfonyl)-3-(4-(3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propoxy)phenyl)acrylamide;

3-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;

4-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)morpholin-3-one

1-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)piperidin-2-one;

(1R,2S)-2-phenyl-N-((1-(2-(4-(piperazin-1-yl)phenoxy)ethyl)azetidin-3-yl)methyl)cyclopropan-1-amine;

(1R,2S)-N-((1-(2-(4-(4-methylpiperazin-1-yl)phenoxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;

1-(4-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)piperazin-1-yl)ethan-1-one;

1-(2-((5-methylpyridin-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

1-(2-((6-methylpyridin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

N-(methylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide;

N-(ethylsulfonyl)-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzamide;

(1S,2R)-N-((1-(2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)oxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;

2-(4-(2-(3-(((1S,2R)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)acetic acid;

4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)benzoic acid

2-(4'-(2-(3-(((1S,2R)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)-[1,1'-biphenyl]-4-yl)-N-(phenylsulfonyl)acetamide;

3-(6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)pyridin-3-yl)-1,3-oxazinan-2-one;

3-(5-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)pyridin-2-yl)-1,3-oxazinan-2-one;

N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(p-tolyl)oxy)ethyl)piperidin-4-amine;

3-(4-(2-(4-(methyl((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;

2-(4-(2-(1-methyl-3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)- λ 4-azetidin-1-yl)ethoxy)phenyl)-N-(methylsulfonyl)acetamide;

N-methyl-1-(2-((6-methylpyridin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

(1R,2S)-N-((1-(2-((6-methylpyridin-3-yl)oxy)ethyl)azetidin-3-yl)methyl)-2-phenylcyclopropan-1-amine;

4-(2-(1-methyl-3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)- λ 4-azetidin-1-yl)ethoxy)-N-(methylsulfonyl)benzamide;

3-(5-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)pyridin-2-yl)-1,3-oxazinan-2-one;

6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-3,4-dihydroquinolin-2(1H)-one;

5-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)indolin-2-one;
1-(2-(3-fluoro-4-methylphenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(quinazolin-4-yloxy)ethyl)piperidin-4-amine;
N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(quinolin-4-yloxy)ethyl)piperidin-4-amine;
N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(pyrimidin-5-yloxy)ethyl)piperidin-4-amine;
1-(2-(3,5-difluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-(3,5-dichlorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-((6-methylpyridazin-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
(E)-3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acrylic acid;
1-(2-(3-fluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-((6-methylpyridin-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-((2-methylpyrimidin-5-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-(4-bromophenoxy)ethyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-2-one;
2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethan-1-ol;
N-(1-(2-(4-(2-oxo-1,3-oxazinan-3-yl)phenoxy)ethyl)piperidin-4-yl)-N-((1R,2S)-2-phenylcyclopropyl)acetamide;
1-(2-methoxyethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-((1,3-dimethyl-1H-pyrazol-5-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-((1-methyl-1H-pyrazol-3-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

3-(4-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethoxy)phenyl)-1,3-oxazinan-2-one;

1-(2-isopropoxyethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

2-(2-fluoro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;

1-(2-(3,5-difluoro-4-methylphenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

1-(2-((5-methyl-1,3,4-thiadiazol-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

2-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)isonicotinic acid;

3-(4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)oxazolidin-2-one;

1-(2-(4-bromophenoxy)ethyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidine-2,6-dione;

N-((1R,2S)-2-phenylcyclopropyl)-1-(2-(pyridin-3-yloxy)ethyl)piperidin-4-amine;

7-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)-2H-benzo[b][1,4]oxazin-3(4H)-one;

6-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)benzo[d]oxazol-2(3H)-one;

1-(2-((5-methylthiazol-2-yl)oxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)isonicotinic acid;

2-(3-chloro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;

2-(3-fluoro-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid;

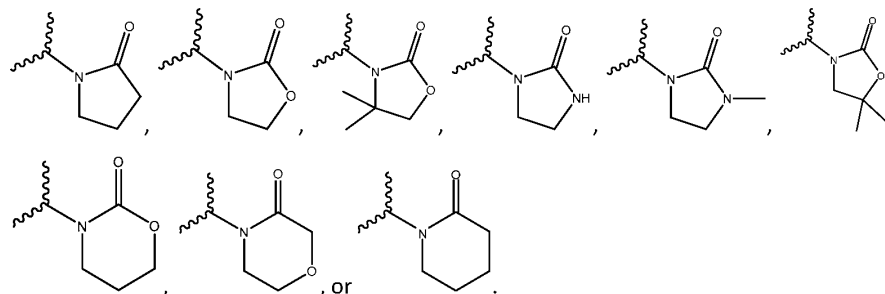
2-(3-methyl-4-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethoxy)phenyl)acetic acid; or

4-(2-(4-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)piperidin-1-yl)ethoxy)benzoic acid;

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein W is $-\text{NR}^4-$ and s is 1 and m is 0.
20. The compound of claim 19, wherein R^5 is aryl optionally independently substituted with one or more R^8 .
21. The compound of claim 20, wherein the aryl is phenyl optionally independently substituted with one or more R^8 .
22. The compound of claim 21, wherein R^8 is heterocyclyl optionally independently substituted one or more $\text{C}_1\text{-C}_3$ alkyl.
23. The compound of claim 22, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, tetrahydropyranyl, 1,3-dioxolanyl, 1,4-dioxanyl, morpholinyl, dimethyl-morpholinyl, thiomorpholinyl, 1,4-dithianyl, or 1,3,5-trithianyl.

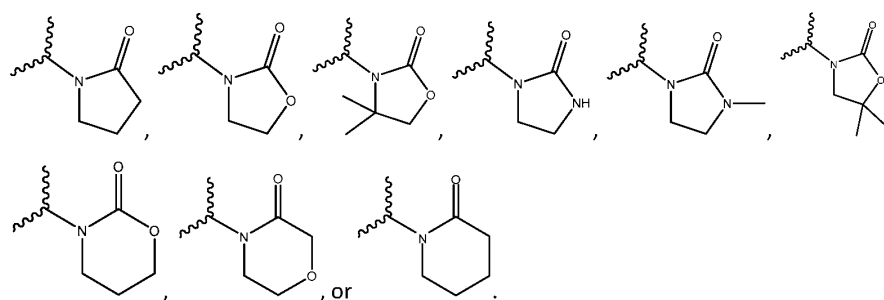
24. The compound of claim 22, wherein the heterocyclyl is:



25. The compound of claim 21, wherein R^8 is halogen, alkyl, $-(\text{CH}_2)_n\text{COOR}^4$, $-(\text{CH}_2)_p\text{C}(\text{O})\text{NR}^4\text{OC}_1\text{-C}_4\text{alkyl}$, $-(\text{CH}_2)_p\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{C}_1\text{-C}_4\text{alkyl}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{cycloalkyl}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^4\text{SO}_2\text{aryl}$, $-\text{CH}=\text{CHC}(\text{O})\text{OR}^4$, $-\text{CH}=\text{CHC}(\text{O})\text{NR}^4\text{SO}_2\text{C}_1\text{-C}_4\text{alkyl}$, or $-\text{CH}=\text{CHC}(\text{O})\text{NR}^4\text{SO}_2\text{aryl}$.
26. The compound of claim 19, wherein R^5 is heteroaryl optionally independently substituted with one or more R^8 .
27. The compound of claim 26, wherein the heteroaryl is pyridyl, 6-methyl-pyridyl, 4-carboxy-pyridyl, dihydroquinolinone, indolinone, quinazolinyl, quinolinyl, pyrimidinyl,

2-methyl-pyrimidinyl, pyridazinyl, 6-methyl-pyridiazinyl, pyrazolyl, 1-methyl-pyrazolyl, 5-methyl-pyrazolyl, 1,3-dimethyl-pyrazolyl, thiazolyl, 5-methyl-thiazolyl, benzo[d]oxazol-2(3H)-one, 2H-benzo[b][1,4]oxazin-3(4H)-one, thiadiazolyl or 5-methyl-thiadiazolyl.

28. The compound of claim 26, wherein the heteroaryl is pyridyl optionally independently substituted with one or more R^8 .
29. The compound of claim 28, wherein R^8 is heterocyclyl optionally independently substituted one or more C_1 - C_3 alkyl.
30. The compound of claim 29, wherein the heterocyclyl is azetidiny, pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, tetrahydropyranyl, 1,3-dioxolanyl, 1,4-dioxanyl, morpholinyl, dimethyl-morpholinyl, thiomorpholinyl, 1,4-dithianyl, or 1,3,5-trithianyl.
31. The compound of claim 29, wherein the heterocyclyl is:



32. The compound of claim 28, wherein R^8 is halogen, alkyl, $-(CH_2)_nCOOR^4$, $-(CH_2)_pC(O)NR^4OC_1-C_4alkyl$, $-(CH_2)_pC(O)NR^4SO_2C_1-C_4alkyl$, $-(CH_2)_nC(O)NR^4SO_2cycloalkyl$, $-(CH_2)_nC(O)NR^4SO_2aryl$, $-CH=CHC(O)OR^4$, $-CH=CHC(O)NR^4SO_2C_1-C_4alkyl$, or $-CH=CHC(O)NR^4SO_2aryl$.
33. The compound of formula (II) of claim 19, wherein R^A is oxo and n is 1 or 2.
34. The compound of formula (II) of claim 19, wherein two R^A groups on different ring atoms together form a C_1 - C_3 bridge in which one of the bridge carbons is optionally replaced with $-NH-$.
35. The compound of claim 19, wherein the compound is
1-anilino-3-[4-[[trans-2-phenylcyclopropyl]amino]-1-piperidyl] propan-2-ol;

1-(N-methylanilino)-3-[4-[[trans-2-phenylcyclopropyl]amino]-1-piperidyl]propan-2-ol;
1-(2-(phenylamino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-(methyl(phenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-((4-bromophenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)piperidin-2-one;
3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one;
4-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)morpholin-3-one;
N-((1R,2S)-2-phenylcyclopropyl)-1-(2-((4-(piperidin-1-yl)phenyl)amino)ethyl)piperidin-4-amine;
1-(2-((4-morpholinophenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(2-((4-(4-methylpiperazin-1-yl)phenyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;
1-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)pyrrolidin-2-one;
3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)oxazolidin-2-one;
1-methyl-3-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)imidazolidin-2-one;
1-(4-(4-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)piperazin-1-yl)ethan-1-one;
3-(4-((2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one;
N,6-dimethyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)pyridin-3-amine;

1-(2-((4-bromophenyl)(methyl)amino)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

3-(4-(methyl(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)phenyl)-1,3-oxazinan-2-one;

1-methyl-3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)urea;

N-methyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)acetamide;

N,2-dimethyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)pyridin-4-amine;

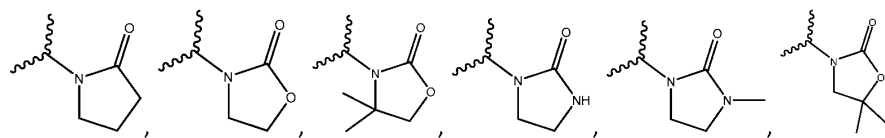
1-(2-(4-bromo-2-fluorophenoxy)ethyl)-N-((1R,2S)-2-phenylcyclopropyl)piperidin-4-amine;

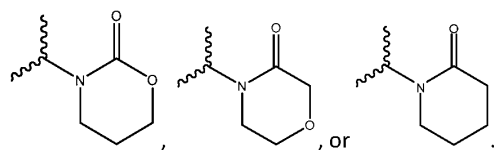
2-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)isonicotinic acid; or

3-((2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)amino)isonicotinic acid;

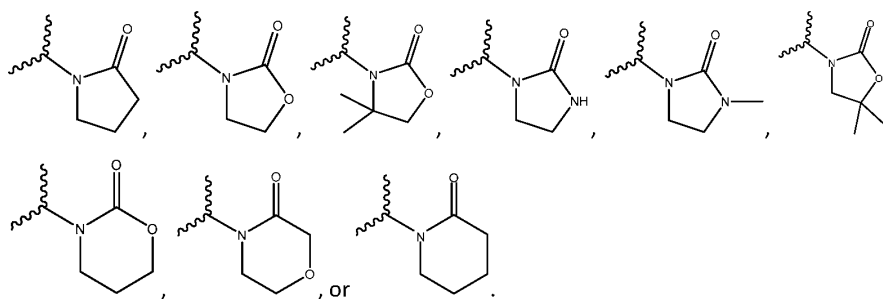
or a pharmaceutically acceptable salt thereof.

36. The compound of claim 1, wherein Y is -C(O)-, s is 0, m is 0, R² is C₁-C₄ alkyl or aralkyl, R³ is hydrogen and R⁶ is heterocyclyl,
37. The compound of claim 36, wherein the heterocyclyl is piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.
38. The compound of claim 37, wherein R² is methyl.
39. The compound of claim 37, wherein R² is benzyl.
40. The compound of claim 36, wherein the heterocyclyl is:

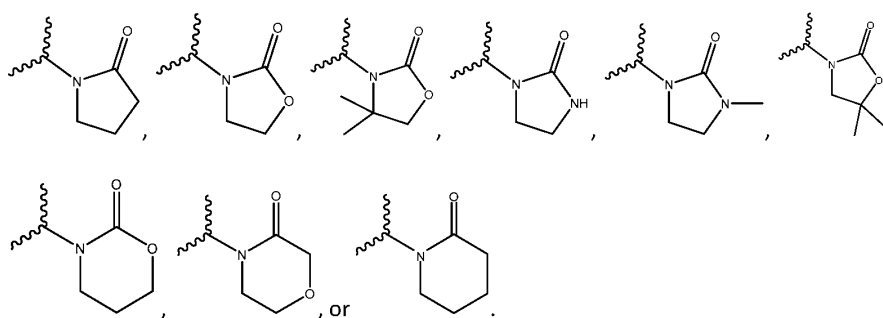




41. The compound of claim 1, wherein Y is -C(O)-, s is 1, m is 0, R² and R³ are each independently hydrogen, and R⁶ is heterocyclyl.
42. The compound of claim 41, wherein the heterocyclyl is piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.
43. The compound of claim 41, wherein the heterocyclyl is:



44. The compound of claim 1, wherein Y is -C(O)-, s is 1, m is 1, R² and R³ are each hydrogen, and R⁶ is heterocyclyl.
45. The compound of claim 41, wherein the heterocyclyl is piperazinyl, 4-methyl-piperazinyl, 4-acyl-piperazinyl, morpholinyl, dimethyl-morpholinyl, or thiomorpholinyl.
46. The compound of claim 41, wherein the heterocyclyl is:



47. The compound of claim 1, wherein Y is -C(O)-, s is 1, m is 1, R² and R³ are each hydrogen, and R⁶ is -NR⁴R⁷.

48. The compound of claim 47, wherein R^7 is alkoxy, $-SO_2C_1-C_4alkyl$, $-SO_2cycloalkyl$, -or SO_2aryl , wherein the cycloalkyl or aryl of each of the $-SO_2cycloalkyl$ and $-SO_2aryl$ may be optionally substituted with one or more R^8 .
49. The compound of claim 36, 42 or 44, wherein the compound is
- 1-morpholino-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;
- N-methoxy-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide;
- 1-morpholino-3-phenyl-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;
- 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanoic acid;
- 1-morpholino-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;
- N-(methylsulfonyl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide;
- 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-(piperazin-1-yl)propan-1-one;
- 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-N-(phenylsulfonyl)propanamide;
- 1-(4-methylpiperazin-1-yl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;
- N-(ethylsulfonyl)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propanamide;
- 3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-thiomorpholinopropan-1-one;
- 1-(4-methylpiperazin-1-yl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butan-1-one;
- 4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-1-(piperazin-1-yl)butan-1-one;
- 1-morpholino-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butan-1-one;

4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)-N-(phenylsulfonyl)butanamide;

4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanoic acid;

N-(cyclopropylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide;

N-(ethylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide;

N-(methylsulfonyl)-4-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)butanamide; or

1-(*cis*-2,6-dimethylmorpholino)-3-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propan-1-one;

or a pharmaceutically acceptable salt thereof.

50. The compound of claim 1, wherein Y is -NR⁴SO₂-, m is 1, R² and R³ are each hydrogen, and R⁶ is C₁-C₆ alkyl, cycloalkyl or aryl, wherein the cycloalkyl or the aryl may be optionally independently substituted with one or more C₁-C₃ alkyl, halogen, haloalkyl, amino or cyano.
51. The compound of claim 50, wherein the compound is
- N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)methanesulfonamide;
- N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)benzenesulfonamide;
- N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)propane-2-sulfonamide;
- N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)propyl)methanesulfonamide;
- N-methyl-N-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)methanesulfonamide;
- N-(2-(3-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)azetidin-1-yl)ethyl)methanesulfonamide;
- N-methyl-N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)methanesulfonamide;

N-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)cyclopropanesulfonamide;

or a pharmaceutically acceptable salt thereof.

52. The compound of claim 1, wherein Y is $-\text{SO}_2\text{NR}^4-$, s is 1, m is 1, R^2 and R^3 are each independently hydrogen and R^6 is C_1 - C_6 alkyl or aryl, wherein the aryl may be optionally independently substituted with one or more C_1 - C_3 alkyl, halogen, haloalkyl, amino or cyano.
53. The compound of claim 46, wherein the compound is
- N-phenyl-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethane-1-sulfonamide; or
- N-methyl-2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethane-1-sulfonamide;
- or a pharmaceutically acceptable salt thereof.
54. The compound of claim 1, wherein Y is $-\text{NR}^4\text{C}(\text{O})\text{NR}^4\text{R}^4$, s is 1, m is 1, R^2 and R^3 are each hydrogen and each R^4 is independently hydrogen or C_1 - C_3 alkyl.
55. The compound of claim 54, wherein each R^4 is C_1 - C_3 alkyl.
56. The compound of claim 55, wherein the compound is 1,1-dimethyl-3-(2-(4-(((1R,2S)-2-phenylcyclopropyl)amino)piperidin-1-yl)ethyl)urea.
57. A pharmaceutical composition, comprising an effective LSD-1 inhibiting amount of a compound of any of claims 1 – 56, and a pharmaceutically acceptable excipient.
58. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any of claims 1 – 56, and a pharmaceutically acceptable excipient.
59. A method for inhibiting LSD1 activity in a cell, comprising contacting the cell in which inhibition of LSD1 activity is desired with an effective LSD-1 inhibiting amount of a compound of any of claims 1 – 56 or pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing the compound of any of claims 1 – 56 or a pharmaceutically acceptable salt thereof.
60. A method for treating cancer comprising administering to a patient having cancer a therapeutically effective amount of a compound of formula (I) or formula (II) of claim 1,

or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents.

61. The method of Claim 60, wherein the therapeutically effective amount of the compound is between about 0.01 to 300 mg/kg per day.
62. The method of Claim 61, wherein the therapeutically effective amount of the compound is between about 0.1 to 100 mg/kg per day.
63. The method of Claim 62, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondilagenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma,

glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

64. The method of Claim 60, wherein the cancer is non-small cell lung cancer.